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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 7/40, 6/00, 7/16, 9/68, 47/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/02136</b> <b>(43) International Publication Date:</b> 22 January 1998 (22.01.98)
<b>(21) International Application Number:</b> PCT/US97/12496 <b>(22) International Filing Date:</b> 16 July 1997 (16.07.97)  <b>(30) Priority Data:</b> 08/683,778      16 July 1996 (16.07.96)      US  <b>(71)(72) Applicants and Inventors:</b> HOMOLA, Andrew, M. [US/US]; 16823 Sorrel Way, Morgan Hill, CA 95027 (US). DUNTON, Ronald, K. [US/US]; 40 Highgate Road, Santa Cruz, CA 95066 (US).  <b>(74) Agents:</b> BAXTER, Stephen, G. et al.; Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Crystal Square Five, 4th floor, 1755 Jefferson Davis Highway, Arlington, VA 22202 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHODS, COMPOSITIONS, AND DENTAL DELIVERY SYSTEMS FOR THE PROTECTION OF THE SURFACES OF TEETH  <b>(57) Abstract</b>  The present invention discloses compositions containing a transfer agent and/or bactericidal compounds, and hydrophobic materials which form, upon application to dental surfaces, adhesive, protective and bacteria-inhibiting barriers.		

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TITLE OF THE INVENTION

METHODS, COMPOSITIONS, AND DENTAL DELIVERY SYSTEMS  
FOR THE PROTECTION OF THE SURFACES OF TEETH

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BACKGROUND OF THE INVENTIONField of the Invention:

The present invention relates to oral hygiene and specifically to methods of treating the oral cavity with a dental delivery systems such as toothpaste, masticables  
10 including chewing gums, dental floss or toothpicks, with improved cleaning, conditioning and antimicrobial properties, which provide the teeth with an impervious protective barrier. The present invention also relates to compositions and dental delivery systems having improved  
15 cleaning, conditioning, and antimicrobial properties, which provide the teeth with an impervious protective barrier. The present invention also relates to compositions and delivery systems useful for sealing and blocking dentinal tubules thus relieving pain and discomfort due to  
20 sensitivity. The present invention also relates to novel cationic surfactants especially suited for use in the present compositions, methods, and dental delivery systems. The present invention also relates to confections, such as candies and mints, which provide teeth with a protective barrier. The present invention also relates to a method for preventing and/or treating gingivitis and to a method for alleviating the sensitivity of teeth.

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Description of the Background:

The oral care industry and health research communities have looked for many years for a way to interdict the attachment, propagation, growth or colonization of bacteria on teeth since adhered bacteria are the start of a pernicious chain of events leading to formation of home care-resistant plaque, calculus, and ultimately, tooth-loss. As people in developed countries live longer, dental care plays a larger role in overall health, and developing countries are becoming more aware of the importance of oral hygiene.

Dental plaque results when cariogenic bacteria (e.g., *Streptococcus mutans*) collect in colonies and form deposits on tooth surfaces. The presence of the bacteria and deposits is extremely detrimental to the health of the tooth for, if left unchecked, they may result in infected gingival tissue, the formation of dental caries and possibly periodontal disease. In extreme cases their presence may even result in the loss of teeth. Many attempts have been made to control or prevent both the occurrence of dental caries and the formation of dental plaque. For example, fluoride solutions or gels have been used. Treatment with these materials is typically performed in a dental office at periodic, but not frequent, intervals. Such treatments are primarily intended to render tooth enamel more resistant to the acid action caused by plaque. They do not, however, result in plaque



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control for an extended period since plaque reestablishes itself on the teeth shortly after ingestion of food.

Even when the frequency of application of such solutions and gels is increased only partial control has been shown. For example, studies wherein a fluoride-containing solution (1% fluoride concentration) was applied four to five times in the course of a year have demonstrated that this technique had only limited success due to the rapid reestablishment of plaque in the oral cavity. Moreover, the daily application of a fluoride gel by means of a custom-fitted polyvinyl mouthpiece for a period of twenty-one months also showed no substantial change in plaque formation among treated and untreated patients (see "Clinical Anticaries Effect of A Repeated Sodium Fluoride Application by Mouthpiece," Journal of the American Dental Association, vol. 75, no. 3, September, 1967, pages 638-644).

For long years the dental research community has sought to develop a way of sealing the teeth against access to dental surfaces by bacteria, acids and other deleterious materials. Good sealants have been developed and are now available, but they require professional application involving thorough cleaning and drying of each tooth prior to application of the sealant and the cost and availability of qualified professionals has meant that the benefits of this technology are not available to many people in the

developed world and essentially to no one in the lesser developed countries.

Proper use of dental floss is necessary to clean the considerable area on the interproximal surfaces of teeth, which cannot be reached by the bristles of a toothbrush.

The purpose of using dental floss is:

1. to dislodge and remove any decomposing food material that has accumulated at the interproximal surfaces that cannot be removed by brushing; and

2. to dislodge and remove as much as possible the growth of bacterial material (plaque) upon the teeth or the superimposed calculus that has accumulated there since the previous cleaning.

The concept of the use of dental floss for cleansing interproximal spaces appears to have been introduced by Parmly in 1819 ("Practical Guide to the Management of the Teeth," Collins & Croft, Philadelphia PA). Parmly suggested the use of waxed silk to clean teeth of persons subject to gingival inflammation. Numerous types of floss were developed and used for cleaning, until finally in 1948 Bass established the optimum characteristics of dental floss (Dental Items of Interest, vol. 70, pp. 921-34, (1948)). Most floss sold at retail today is also "waxed" to assist penetration to interproximal regions; as the "cord" effect described by Bass makes the floss bundle difficult to force between closely spaced teeth.

From 1960 through 1962, numerous clinical studies reported that there is no clinical difference as to plaque removal and gingivitis scores between waxed and unwaxed dental floss. O'Leary in 1970, and Hill et al. in 1973, found no difference in the interproximal cleansing properties of waxed or unwaxed dental floss. This was reconfirmed in 1982 by Lobene et al. (Clinical Preventative Dentistry, Jan-Feb (1982)) who showed no significant clinical difference on plaque and gingivitis scores. Similar results. i.e., no clinical difference between waxed and unwaxed floss with respect to reduced gingival inflammation were shown by Finkelstein in 1979 (J. Dent. Res., vol. 58, pp. 1034-1039 (1979)). No differences in gingival health were shown by Wunderlich in 1981 (J. Dent. Res., vol. 60A, p. 862 (1981)). No differences in plaque removal were reported by Schmidt et al. in 1962 (J. Dent. Res. (1962)) with flosses of various types. Stevens in 1980, studied floss with variable diameters and showed no difference in plaque and gingival health. Carter et al., Va Dent. J., vol. 52, pp. 18-27 (1975), studied professional and self-administered waxed and unwaxed floss and found that both significantly reduced gingival bleeding of interproximal and gingival sulci. Unwaxed floss appeared slightly, but not significantly more effective.

In view of this clinical work, it is not surprising that most of the dental floss sold today is bonded and/or waxed. The "bonding" in the yarn industry today is used

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more to facilitate processing and production during floss manufacture and packaging than for "flossing" reasons. Since clinical tests show no difference between waxed and unwaxed floss, the floss industry has been comfortable with the yarn industry's propensity to use bonding agents in floss.

In any event, most people in the world do not floss their teeth. Instead, sticks or toothpicks are often used to clean their teeth.

Maetani et al, U.S. Patent No. 2,504,228, describe a metallic dental casting coated with a PTFE coating. The PTFE coating is applied from a solution. The PTFE may also be applied from a suspension (an organosol) that may include other resins as well, such as, for example a silicone.

Lorch in U.S. Patent No. 4,776,358 describes a flossing tape that carries its own supply of a dentifrice. The tape may be made of a confronting pair of laminae films that are microporous. The dentifrice is positioned between confronting surfaces of the two laminae, and the longitudinal opposite edges of the two laminae are sealed together. In use, the dentifrice flows out through the pores of the laminae. The laminae may be films of PTFE. The dentifrice is conventional, generally a commercially available material,

Blass in U.S. Patent No. 4,996,056 describes coating a dental floss or tape with a mixture of wax and PTFE powder.

La Rochelle in U.S. Patent No. 4,157,386 discloses a lozenge which coats the surfaces of the teeth and which contains fluoride ion, a polishing agent, and a vegetable oil.

Gaffar et al in U.S. Patent No. 5,344,641 discloses a dentifrice containing an antibacterial agent, an antibacterial enhancing agent, a polishing agent, and a solubilizing agent. The antibacterial enhancing agent is an anionic film-forming material thought to attach to tooth surfaces thereby preventing bacterial attachment and enhancing delivery of the antibacterial agent to tooth surfaces.

Raaf et al in U.S. Patent No. 4,169,885 discloses a filled capsule which has an outer hydrophilic active substance and an inner core containing a hydrophobic substance, a fluoride source and an antimicrobial substance. Upon consumption of the capsule, the hydrophilic substance is believed to fix the hydrophobic active substance to the teeth.

Hill et al in U.S. Patent No. 5,165,913 discloses dental floss which contains a surfactant, silicone and a chemotherapeutic agent. The chemotherapeutic agent is delivered upon splaying of the floss. The surfactant and the silicone are believed to coat the teeth, provide a smooth feeling to the user, and prevent the attachment of bacteria.

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Chang in U.S. Patent No. R 31,787 discloses an elution reducing dentifrice containing a membrane-forming material. Application of the membrane-forming material is believed to inhibit the elution of a previously applied therapeutic agent (i.e., fluoride).

Curtis et al in U.S. Patent No. 4,528,182 and Crawford et al in U.S. Patent No. 4,490,353 disclose an antiplaque dentifrice composition containing a quaternary ammonium compound, a betaine surfactant, polyethylene glycol and an abrasive. The presence of the betaine surfactant is believed to increase the foaming of the dentifrice and to prevent the deactivating of the quaternary ammonium compound.

However, none of these approaches or any other available product or technology has proven to be satisfactory since all prior attempts to produce a consumer-applied protective sealant have resulted in systems which apply a mono-layer - a single molecular layer - of material which is soon removed by chemical or mechanical action so that efficacy, if any, is of exceedingly short duration. Thus, there remains a great need for improved methods, compositions and dental delivery systems which are effective for the prevention of bacterial adhesion to teeth, exhibit antimicrobial properties and can be applied by traditional or acceptable means by the consumer as well as the professional to teeth which need not be dry or particularly clean.

A significant portion of the human population experiences pain or discomfort due to sensitivity of the teeth to heat, cold or pressure. Many products promise or provide short term relief but more lasting benefits have been elusive. Compositions and methods of the present invention may afford many sufferers longer term relief as dentinal tubules are occluded or effectively blocked more enduringly.

#### SUMMARY OF THE INVENTION

Accordingly, it is one object of the present invention to provide novel dental delivery systems which exhibit improved antimicrobial properties.

It is another object of the present invention to provide novel toothpastes which exhibit improved protective, antimicrobial and anti-sensitivity properties.

It is another object of the present invention to provide novel masticables, including chewing gums and chewable matrices of polymeric materials, which deliver the benefits of the compositions of the present invention.

It is another object of the present invention to provide novel dental floss which exhibits improved protective, antimicrobial and anti-sensitivity properties.

It is another object of the present invention to provide novel toothpicks which exhibit improved protective, antimicrobial and anti-sensitivity properties.

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It is another object of the present invention to provide a method for treating teeth which confers improved protection, microbial resistance and anti-sensitivity benefits on the teeth.

It is another object of the present invention to provide a method for treating teeth which confers protection, microbial resistance and anti-sensitivity benefits on the teeth.

It is another object of the present invention to provide a method for treating teeth which results in a reduced ability of bacteria to adhere to teeth.

It is another object of the present invention to provide novel compositions which confer improved protection, microbial resistance and anti-sensitivity benefits on teeth.

It is another object of the present invention to provide novel compositions which confer prolonged protection, microbial resistance and anti-sensitivity benefits on teeth.

It is another object of the present invention to provide novel compositions which result in a reduced ability of bacteria to adhere to teeth.

It is another object of the present invention to provide novel cationic surfactants useful in such methods, compositions, and dental delivery systems.

It is another object of the present invention to treat/coat dental surfaces with an enduring, inert.



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continuous, hydrophobic material which will constitute a physical barrier against access to the tooth surface by bacteria, acids, food remnants, etc., and prevent loss of fluorine by elution from dental surfaces.

It is another object of the present invention to provide such barriers, for deposition onto dental surfaces, which include materials which enhance the purposes of oral hygiene such as sources of fluoride, substances which are shown to inhibit the attachment, propagation, growth or colonization of undesirable bacteria, anti-septic or antibiotic materials, detergents, anti-inflammatories, anti-sensitivity compounds, and other such active agents.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that application of a composition which comprises:

(a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of a transfer agent; and

(b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material  
to teeth results in a prolonged reduction in the ability of bacteria to adhere to teeth.

Thus, the present invention provides new compositions which bond to substrates, especially to those dental (tooth) surfaces having pits, fissures, depressions, cracks, dental tubules, interstices or irregularities. The compositions conform to the topography of the surfaces of

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the teeth, depositing protective barrier materials on the surfaces of the teeth.

The methods of this invention result in the bonding of waxy materials to substrates, such as teeth. The application of the present compositions to dental floss or dental tape, according to the methods of the present invention, provides an appropriate combination of bonding to the floss or tape together with transferability of the compositions onto and into the surfaces of the teeth during use of the floss or tape.

The present invention also relates to a composition and method which is useful for relieving pain and discomfort associated with hypersensitive teeth. More particularly, the invention relates to the use of an inert, hydrophobic and strongly adhering barrier film capable of isolating sensitive dentin and dentinal tubules from mechanical, thermal, chemical, and osmotic stimuli. When the surface of the tooth is damaged or eroded, the dentinal tubules, which lead from the pulp to the surface of the dentin, provide a pathway for transport of oral fluids to the pulpal nerves as induced by changes in temperature, pressure and ionic gradients. By sealing and blocking the tubules, the external stimuli have a diminished effect resulting in reduced pain and discomfort. Desensitizing agents may also be incorporated in the composition to enhance the magnitude and endurance of the desensitizing effect. Particulates added to block or occlude the

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dentinal tubules may be selected from those having porosities which may serve as reservoirs for some of the usual desensitizing materials such as the salts of strontium, potassium, etc.

Also disclosed is the incorporation into the barrier film various anti-hypersensitivity agents such as the salts of strontium and potassium and other water-soluble compounds known to be effective in treatment of dental hypersensitivity. Specifically, the present invention contemplates the addition to the formulations in all delivery systems, including toothpastes, chewing gums, dental flosses and tapes, dental sticks, toothpicks, etc., of water-insoluble porous, inorganic or polymeric beads preferably from within the size range of 1 micron to 100 microns and having a network of interconnecting pores in the size range of from about 1 micron to 20 microns and impregnated with one or more of the water-soluble anti-hypersensitivity agents. The use of such porous beads allows for a controllable delivery of active ingredients with the release rate determined by the average pore size of porous particulates.

The compositions of the present invention may be applied to dental surfaces using toothbrushes, both manual and automated, having either "natural", nylon, or other fibrous, multifilament or monofilament bristles. The methodology employed for applying the barrier materials and duplex films to the bristles may be as described below as

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used for application to dental flosses and tapes, or may be applied by application of the compositions of the present invention directly to the brush from a tube or other container as is done with conventional toothpastes.

In one embodiment, the compositions of the present invention are applied to dental surfaces by a chewable delivery system comprising a transfer agent and barrier material, both incorporated into a chewing gum base. Chewing gums available today generally contain a water-insoluble base portion and water-soluble flavor portion, the latter of which is dissipated over a period of time during mastication of the gum. The base portion is formulated from natural gums and elastomers and/or synthetic gums and elastomers such as polyisobutylene, isobutylene-isoprene copolymers and butadiene-styrene copolymers or mixtures thereof.

The present invention contemplates the addition to the gum base of ingredients comprising one or several compounds from the family of 'barrier' materials and one or more of the transfer and/or 'active' agents as described in the section on "Active-Agents". During masticating, the substances incorporated in the gum base are released from the gum and deposited onto dental surfaces providing a physical barrier against access to the tooth surface by bacteria, acids and other deleterious substances.

In another embodiment of the present invention the compositions of the present invention are applied to dental

surfaces by a chewable delivery system comprising 'transfer', 'active' agents and 'barrier' materials incorporated into pores of microporous plastics or naturally occurring materials which can be molded into various forms and shapes at high production rates or easily worked into fabricated products from sheet or pellet forms. The microporous matrices of appropriate material have open and interconnecting networks of pores with average pore sizes of 1 micron through 1000 microns and a chewable structure adjusted by a proper choice and composition of polymers and/or elastomers.

The compositions of the present invention may also be applied to dental surfaces using any of a variety of interdental or dental appliances of wood, plastic, metals, etc. A stick-like appliance may be covered at one or both ends with any material suitable for coating with the composition of the present invention. The appliance may be similar to the presently marketed interdental appliances of Johnson & Johnson known as "Stimudents", in a configuration similar to the popular cotton "Q-Tip" swabs, or in a configuration in which the applicator is inserted in or otherwise attached to an appropriate holder.

The materials used for covering the applicator-ends of the appliance may include, for example: a) natural or synthetic yarn, filaments, or other fibrous material either as such or assembled as a textile, or to any braided, stranded, woven, non-woven, knitted, matted, felted, etc.

material, in which the materials of the composition of the present invention (hereinafter MCPI) are held among or between the fibers or the strands of the materials; b) foam-like or otherwise porous materials in which the MCPI are held within pores or apertures; or c) non-porous, non-fibrous materials such as some types of wood, plastic, metal, etc.

In the Examples, below, the surfaces of wooden toothpicks were coated and a film of MCPI transferred to the wet surfaces of glass microscope slides. The toothpicks were merely dipped and dried, using the same techniques as for dental floss.

Thus, in one embodiment of the present invention, the surfaces of the teeth are coated with a material which forms a "duplex film" composed of a strongly electrostatically-adhesive monolayer of a positively charged polyelectrolyte (such as, for example, polyethyleneimine, PEI) reacted with a monolayer of fatty acid molecules. The fatty acid molecules bond to the PEI layers with their carboxylic groups while the hydrocarbon parts of the fatty acid chains form a highly hydrophobic interface that is compatible with the hydrophobic barrier materials.

In addition to fatty acids, other compounds having low surface tensions and water repelling properties that can be used in the practice of the present invention include polymethylalkyl siloxanes such as, for example, polymethylhexadecylsiloxane, and polyfluoroalkyl methylsiloxanes (for

example, polymethyl-3,3,3-trifluoropropyl siloxane). These further enhance the hydrophobicity of the duplex films and facilitate the transfer of hydrophobic barrier materials. Saturated hydrocarbons such as waxes, including beeswax, carnauba wax, and petroleum waxes such as the paraffins, and fluorocarbon polymers may also be used.

In other applications, the duplex film can be replaced by a single monolayer composed of a low molecular weight surfactant in which positively charged groups react with the surfaces of the teeth and the water repelling part of the chain forms a highly hydrophobic interface. Examples of such surfactants are cetyltrimethylammonium bromide (CTAB), hexadecyltrimethylammonium bromide (HDTAB), and various amines and quaternary amines, of which a good example is Hyamine-1622 quaternary amine.

The compositions of the present invention are generally semi-solid or solid state materials which may be applied to dental surfaces by brush, masticables including chewing gum, dental floss, dental tape, interdental appliances, swabs, sticks, toothpicks and all other applicators or methods of application by which semi-solid or solid materials may be brought into contact with dental surfaces. All such applicators or methods of application are hereafter referred to as "Applicators".

As shown in the schematic illustrations given in Figures 1 and 2a and b, the compositions of the present invention, as applied to dental surfaces, provide a

multi-stratum protective coating (hereafter called the "Protective Coating: or "PC"), as follows:

(1) The transfer agent stratum has dual functionality, being composed of materials having some molecular segments or parts of a polymeric chain which are positively charged and other such segments which exhibit hydrophobic characteristics.

Three categories of transfer agent materials include:

(a) monomeric cationic surfactants, (b) cationic polyelectrolytes or their products or complexes with organic or inorganic acids, and (c) polypeptide-like materials having a preponderance of positively charged functional groups.

(2) Barrier Stratum: to the hydrophobic components of the transfer agent stratum, a hydrophobic, inert material (hereafter called the "barrier" material), such as a wax is adhered. The thickness of the barrier stratum is typically between about  $1\mu$  and about  $10\mu$ .

In preferred embodiments the PC may further provide:

(3) Anti-Bacterial function: within the barrier stratum may be blended therapeutic, hygienic, anti-sensitivity, including particulate materials or otherwise desirable materials which are released as they are exposed on the surfaces of the barrier stratum. One of the materials typically blended into the barrier material is a substance or substances shown to inhibit the attachment or otherwise defeat the propagation, growth or colonization of



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deleterious bacteria such as *Streptococcus mutans*, *S. sobrinus*, etc. As noted above the composition may further comprise other active agents. Any such substance is referred to hereafter as an "Active-Agent" or "A-A" material.

Thus, the present invention makes possible the first significant improvement in consumer or home dental care in decades. Specifically, the present invention provides the following advances:

I. Application of a composition of the present invention to teeth provides a continuous, hydrophobic, inert barrier which prevents acids, staining materials, (Figure 9 shows several staining materials on an untreated surface on the left, 9a, compared with the same materials on a surface treated with a composition of the present invention on the right, 9b), food particles, bacteria and all other materials from gaining access to the treated dental surface and thus provides protection against all of the usual destructive processes - including the loss of fluorine by elution. In addition, these deleterious substances attach themselves less readily to the barrier than they do to unprotected tooth surfaces.

II. Any bacteria or other debris which do attach to the protective barrier are easily removed by toothbrushing, pressure water cleaning, flossing and even by vigorous mouth rinsing since the amorphous barrier is easily cleaved or sheared, removing the outermost material but leaving

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some of its protective barrier remaining. Without such protection, bacteria which have attached themselves to the tooth surface soon become impossible to dislodge by toothbrushing or flossing and must be professionally removed. Since bacterial attachment begins to take place soon after each meal, the barrier is of great prophylactic significance.

III. The barrier material readily fills and thus seals pits, fissures and cracks which are the favorite venues for bacteria colonization and plaque development. The barrier remains in place until mechanically removed from these pits, etc. and thereby provides protection which is even more extended in the vulnerable areas, since the barrier material is not removed from pits, fissures, etc. as easily as it is from smoother tooth surfaces in the ordinary course of abrasive action by the tongue, mastication of food, toothbrushing, etc.

IV. By the addition to the barrier composition of an antibacterial material, 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine, which is obtainable from Angus Chemical Co. under the trade name Hexetidine being an example of a most especially preferred active agent, bacterial attachment to the barrier surface is reduced by an estimated 90% or more, compared to the number and density of bacteria which attach to unprotected tooth surfaces. Of course, those bacteria which do attach are still easily removed by typical consumer activities such as

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toothbrushing and flossing. In addition, it appears that the hexetidine migrates or diffuses from the barrier material onto tooth surfaces which the barrier didn't reach, providing some protection to these hard to reach and most vulnerable areas.

V. Importantly, the benefits of the present invention can be delivered by a broad range of application methods, e.g., toothpaste, chewing gum, masticable matrices other than traditional chewing gum, dental floss and tape, Q-tip<sup>®</sup>-like swabs, toothpicks, interdental appliances like Stimudents<sup>®</sup>, pre-coated toothbrushes, and any other applicators for consumer or professional use that one wishes to use. The only criterion is that it must be able to bring a waxy material into contact with dental surfaces.

Thus, application of the present compositions is effective to treat/coat dental surfaces with an enduring, inert, continuous, hydrophobic composition which constitutes a physical barrier against access to tooth surfaces by bacteria, acids, food remnants, etc., and prevents loss of fluorine by elution from dental surfaces. In addition, significantly fewer bacteria attach to the barrier than attach to unprotected tooth surfaces. More importantly, bacteria and other materials which attach to the barrier are easily removed by toothbrushing, dental flossing, pressure water cleaning and even vigorous mouth rinsing since the amorphous barrier material is readily

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cleaved or sheared with little effort. Even after the removal of such surface materials, barrier materials remain to continue to provide protection.

On application and thereafter, the barrier materials of the present invention are forced to conform to the topography of the dental surfaces on which they are applied. Especially important, the barrier materials fill the pits, fissures, cracks and other imperfections in dental surfaces, thus blocking those sites in which bacteria are most frequently found and from which they are most difficult to remove. And in such sites, the barrier materials are least subject to removal by the usual oral sources of abrasion and surfaces activities such as movements of the tongue, toothbrushing, mastication, etc. and thus provide the most enduring protection where it is most needed. In addition the adherent characteristic of the compositions of the present invention, the semi-solid or thick paste consistency thereof plus the ability to add particulate materials to the compositions, which materials occlude or block dentinal tubules, provide enduring relief from the pain of dental sensitivity from which so many people suffer.

In a preferred embodiment the barrier material includes agents which enhance the purposes of oral hygiene such as substances which are: (a) shown to enhance the inhibition of attachment, propagation, growth or colonization of undesirable bacteria. (b) other germicidal,

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antiseptic or antibiotic materials, (c) anti-inflammatories, (d) anti-sensitivity materials, (e) particulates which block or occlude dentinal tubules and which assist in cleaning dental surfaces by abrasion, which particulates may be selected from those having porosities appropriate for use as reservoirs for desensitizing agents, and (f) materials which flavor or otherwise enhance the enjoyment of using the compositions of the present invention.

Using one of the most preferred embodiments of the present invention, in which a heterocyclic nitroparaffin-derived material, such as hexetidine, is blended into the barrier composition, bacterial attachment on the protective barrier is reduced by  $\geq 90\%$  as compared with unprotected tooth surfaces. Those few bacteria which may attach to the barrier surface are removable with gentle shearing action.

#### BRIEF DESCRIPTION OF THE DRAWINGS

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same become better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

Figure 1 is a partial section, taken in a horizontal plane, through a coated human tooth, showing the irregular tooth surface, the conformation of the coating to the tooth surface and its relative thickness, all on a much enlarged

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scale. The hydrophobic barrier film, containing antibacterial and other functional agents, conforms to the substrate and fills pits, fissures, cracks and other irregularities of the tooth surface. The transfer layer facilitates adhesion of the hydrophobic barrier film to the tooth surface;

Figures 2a and b are enlarged views of the coated tooth surface, showing the area of the tooth surface in Figure 1, to demonstrate the electrostatic charge distribution at the interface between the tooth surface and the transfer agent. This figures illustrates the mode of attachment of the transfer agent to the negatively charged tooth surface. (a) The molecules of the positively charged surfactant form a dense monolayer which attaches to the negatively charged substrate. The alkyl groups of the transfer agent face away from the surface. (b) Polyamine molecules adsorb to the substrate with their hydrophobic side groups facing away from the hydrophilic tooth surface;

Figure 3 shows the application of a composition according to the present invention to a tooth by a cotton swab;

Figures 4a and b are photomicrographs of an untreated tooth (Figure 4a) and a tooth treated according to the present invention (Figure 4b) after exposure to bacteria-rich media for 48 hours;

Figure 5 shows the application of a composition according to the present invention to a tooth by a toothbrush;

Figures 6a and b are photomicrographs of an untreated tooth (Figure 6a) and a tooth treated according to the present invention (Figure 6b) after exposure to bacteria-rich media for 48 hours;

Figure 7 shows the application of a composition according to the present invention to a tooth by dental floss;

Figures 8a and b are photomicrographs of an untreated tooth (Figure 8a) and a tooth treated according to the present invention (Figure 8b) after exposure to bacteria-rich media for 48 hours; and

Figures 9a and b show the appearance of staining materials on an untreated glass slide (Figure 9a) and a slide treated according to the present invention (Figure 9b).

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Thus, in a first embodiment, the present invention provides novel compositions which contain:

- (a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of a transfer agent; and
- (b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material.

Preferably, the present composition contains:

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(a) 3 to 5 wt.%, based on the total weight of (a) and (b), of a transfer agent; and

(b) 95 to 97 wt.%, based on the total weight of (a) and (b), of a barrier material.

#### THE TRANSFER AGENT FUNCTION

To adhere a hydrophobic barrier material to a wet, hydrophilic, negatively charged tooth surface, a bi-functional transfer agent material is employed. This material has some active groups which are electrostatically positively charged and some active groups which are compatible with the hydrophobic materials of the barrier stratum.

Useful transfer agent materials include various cetyl amine compounds, various diamines (including for example, Duomeens and Ethoduomeens), nitroparaffin-derived heterocyclic amines, and quaternary ammonium compounds. Also useful are compounds of certain cationic polyelectrolytes, invented for the purposes of the present invention and introduced herewith, including, for example, polyethyleneimine (PEI) derivatized with varying concentrations of fatty acids such as, for example, stearic acid, palmitic acid, oleic acid, etc.

Certain of these transfer agents also inhibit the attachment or otherwise defeat the propagation, growth or colonization of bacteria such as, for example, *Streptococcus mutans* and *Streptococcus sobrinus*, when added



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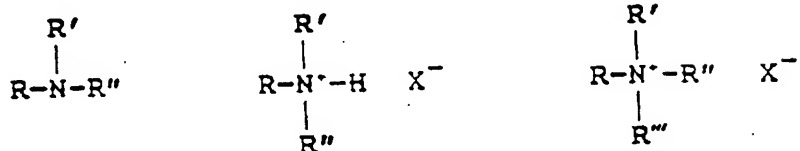
in appropriate concentrations so as to be able to function as a transfer agent and also perform the A-A function.

Some substances, notably some of the bifunctional amine hydrofluorides and specifically the quaternary ammonium fluorides have been used in prior art to produce a mono-layer of bi-polar material adhered to the dental surfaces as an end in itself. But experimentation suggests that the resulting single molecular layer is insufficient to provide a durable functional barrier against attachment of bacteria or to interdict access to tooth surfaces by acids, etc.

#### Transfer Agent Materials:

Cationic transfer agent materials useful in the present invention are believed to attach to tooth surfaces via a complexing interaction between the cationic portion of the material and the proteinaceous portion of the tooth and thus predispose or condition the surface of the tooth so that a waxy material will then adhere to the surface. Surface active materials that are capable of strong bonding to the negatively charged and hydrophilic surfaces of human teeth include various straight-chain alkylammonium compounds, cyclic alkylammonium compounds, petroleum derived cationics, and polymeric cationic materials.

## a) Straight-chain alkylammonium compounds



R represents a long ( $\text{C}_{8-20}$ ) alkyl chain which may be substituted with one or more hydroxy groups,  $\text{R}'$ ,  $\text{R}''$ , and  $\text{R}'''$  each independently may be either a long ( $\text{C}_{8-20}$ ) alkyl chain which may be substituted with one or more hydroxy groups or a smaller ( $\text{C}_{1-4}$ ) alkyl groups which may be substituted with one or more hydroxy groups or aryl ( $\text{C}_{6-10}$ ) groups or hydrogen, and  $\text{X}^-$  represents an anion such as chloride or fluoride. These schematic formulas are given for the purpose of defining the classes of compounds and represent the simplest concepts of cationic transfer agents whereby one or more hydrophobic alkyl groups are linked to a cationic nitrogen atom. In many instances the linkage is more complex as, for example, in  $\text{RCONHCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ . In addition, cationic transfer agents may contain more than one cationic nitrogen atom such as the following class of compounds  $\text{RNHCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  and derivatives thereof.

Representative examples of compounds according to the above formulas are:

cetyl trimethylammonium chloride (CTAB),  
 hexadecyltrimethylammonium bromide (HDTAB),  
 stearyl dimethylbenzylammonium chloride,  
 lauryl dimethylbenzylammonium chloride,  
 cetyl dimethylethylammonium halide.

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cetyl dimethylbenzylammonium halide,  
cetyl trimethylammonium halide,  
dodecyl ethyldimethylammonium halide,  
lauryl trimethylammonium halide,  
coconut alkyltrimethylammonium halide,  
N,N-C<sub>8-20</sub>-dialkyldimethylammonium halide, and specifically  
compounds such as bis(hydrogenated tallow alkyl)  
dimethylammonium chloride which is known to adsorb onto the  
surface with hydrophobic groups oriented away from it, 2-  
hydroxydodecyl-2-hydroxyethyl dimethyl ammonium chloride  
and N-octadecyl-N,N',N'-tris-(2-hydroxyethyl)-1,3-  
diaminopropane dihydrofluoride.

b) Cyclic Alkylammonium Compounds

A further preferred group of compounds of the present invention which have been found to be applicable includes a class of surface-active quaternary ammonium compounds in which the nitrogen atom carrying the cationic charge is part of a heterocyclic ring. Suitable compounds, for example, are as follows:

laurylpyridinium chloride or bromide,  
tetradecylpyridinium bromide,  
cetylpyridinium halide (chloride, bromide or fluoride).

c) Petroleum Derived Cationics

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Typical basic amines are derived from petroleum-based raw materials such as olefins, paraffins, and aromatic hydrocarbons and include compounds with at least one aliphatic carbon chain containing six or more carbon atoms attached to the nitrogen. Thus, amine salts, diamines, amidoamines, alkoxyated amines, and their respective quaternary salts are applicable.

Preferred compounds of this type include tallow or coco alkyl substituted 1,3-propylene diamines sold by Witco under the trade names of "Adogen" and "Emcol" and similar diamines sold by Akzo under the trade name "Duomeen" and their polyethenoxy derivatives under the trade names of "Ethomeen" and "Ethoduomeens".

#### d) Polymeric Amines

Suitable polymeric amines comprise a class of polymers containing ionic groups along the backbone chain and exhibit properties of both electrolytes and polymers. These materials contain nitrogen, of primary, secondary, tertiary or quaternary functionality in their backbone and may have weight average molecular weights as low as about 100 or higher than about 100,000. Representative of these polymeric cationic transfer agents are the following: polydimeryl polyamine (General Mills Chemical Co.), polyamide (trade name "Versamide"), polyacrylamides,

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polydiallyldimethylammonium chloride ("Cat-Floc"),  
polyhexamethylene biguanide compounds as sold under the  
trade name "Vantocil", and also other biguanides, for  
example those disclosed in U.S. Patent Nos. 2,684,924,  
2,990,425, 3,183,230, 3,468,898, 4,022,834, 4,053,636 and  
4,198,425,  
1,5-dimethyl-1,5-diazaundecamethylene polymethobromide  
("Polybrene" from Aldrich),  
polyvinylpyrrolidone and their derivatives,  
polypeptides,  
poly(allylamine) hydrochloride,  
polyoxyethylenated amines, and specifically,  
polyethyleneimine ("Polymin" from BASF),  
and a class of related and surface active cationic polymers  
prepared by converting a fraction of the amino groups to  
their acyl derivatives. The polyethyleneimine is first  
condensed with less than the stoichiometric quantity of  
acid halides thus alkylating some of the amino groups and  
the remaining amino groups are then condensed with hydrogen  
halides such as hydrogen chloride or, preferentially,  
hydrogen fluoride. The surface activity of these compounds  
vary with the number of amino groups which are acylated,  
and with the chain length of the acylating group RCO-. The  
condensation reaction is typically performed with stearic  
or oleic acid chlorides in the presence of a solvent  
containing metal fluoride, preferentially silver fluoride,

in such a manner that silver chloride formed in the reaction precipitates from the solvent (see Example XV).

Also suitable, for the purpose of this invention, are cationic derivatives of polysaccharides such as dextran, starch or cellulose, for example, diethylaminoethyl cellulose ("DEAE-cellulose"). Examples of applicable copolymers based on acrylamide and a cationic monomer are available commercially under the trade name RETEN from Hercules Inc., or under the name FLOC AID from National Adhesives. Particular examples of such polymers are FLOC AID 305 and RETEN 220. Similarly useful are acrylamide-based polyelectrolytes as sold by Allied Colloids under the trade name PERCOL. Further examples of suitable materials are the cationic guar derivatives such as those sold under the trade name JAGUAR by Celanese-Hall.

A further preferred group of compounds which comprises a class of water-insoluble polymers, having nitrogen atoms in their molecules, are quaternary polymers of quaternary ammonium type, betaine type, pyridylpyridinium type or vinylpyridinium-type. Examples are as follows;

- poly(vinyl-benzylmethyllaurylammonium chloride),
- poly(vinyl-benzylstearylbetaine),
- poly(vinyl-benzyllaurylpyridylpyridinium chloride),
- poly(vinyl-benzylcetylammonylhexyl ether) and
- quaternized polyoxyethyleneated long chain amines, with the general formula  $RN(CH_3)[(C_2H_4O)_xH]_2(+) A(-)$ , where  $A(-)$  is

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generally chloride or fluoride,  $x$  is a number from 1 to 20, and  $R$  is  $C_{8-22}$ -alkyl.

These cationic materials, by reacting with dental surfaces, produce strongly hydrophobic films onto which hydrophobic barrier materials are easily transferred by brushing, rubbing, smearing, or burnishing.

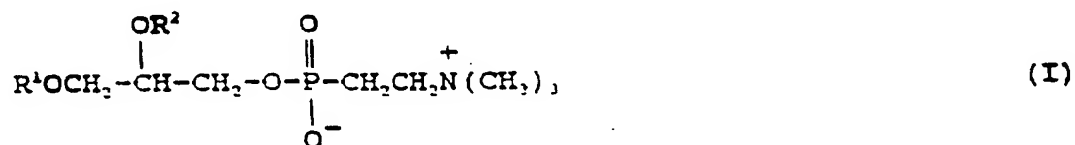
It is important that the reason for this transferability be understood. The surfaces of human teeth are normally hydrophilic, negatively charged, and are "lubricated" by a hydrated biofilm composed of bacteria and other bioorganisms. The transfer and adhesion of the barrier materials onto such dental surfaces is difficult or practically impossible unless the biofilm is modified by a material that is hydrophobic and therefore compatible with the barrier materials.

In a preferred embodiment, the transfer agent, a cationic surfactant, is a polymer which contains a nitrogen atom in a repeating unit and in which a portion of the nitrogen atoms are quaternized by formation of a salt with a  $C_{8-20}$  fatty acid, preferably a  $C_{12-20}$  fatty acid. Examples of such polymeric cationic surfactants include polyacrylamides, polyvinylpyridines, or polyamines, e.g., poly(ethyleneimine), in which from 5 to 95 mole%, preferably 40 to 60 mole%, of the nitrogen atoms have been quaternized by formation of a salt with a fatty acid. Typically such polymers will have a weight average molecular weight of 600 to 60,000, preferably 600 to 1,800.

In a particularly preferred embodiment, the cationic surfactant is a polymer which contains a nitrogen atom in a repeating unit and in which a first portion of the nitrogen atoms are quaternized with a C<sub>8-20</sub> fatty acid, preferably a C<sub>12-20</sub> fatty acid, and a second portion of the nitrogen atoms are quaternized by forming a salt with HF. Examples of such polymeric cationic surfactants include polyacrylamides, polyvinylpyridines or polyamines, e.g., poly(ethyleneimine), in which from 5 to 95 mole%, preferably from 40 to 60 mole %, of the nitrogen atoms are converted to their acid derivatives by reaction with stearic or oleic acid chlorides, and from 5 to 95 mole%, preferably from 40 to 60 mole%, of the nitrogen atoms are quaternized with HF. In this case, the polymeric cationic surfactant will have a weight average molecular weight of 600 to 60,000, preferably 600 to 1,800.

In another preferred embodiment, the cationic surfactant is a C<sub>8-20</sub>-alkylamine which has been quaternized with HF, such as cetylamine hydrofluoride.

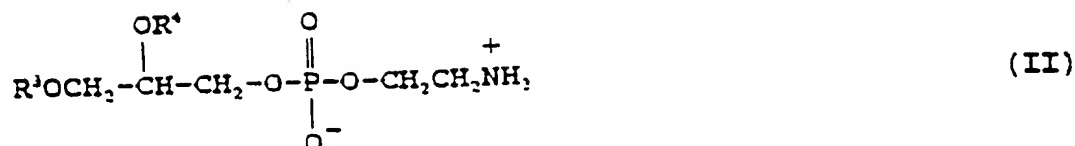
In another preferred embodiment, the transfer agent is lecithin. In the present context, the term lecithin includes compounds of the formulae (I) and (II)



and



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in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ , and  $\text{R}^4$  are each, independently of each other, a  $\text{C}_{12-22}$  saturated or unsaturated alkanoyl group, such as stearoyl, palmitoyl, oleoyl, palmitoleoyl, linoleoyl, linolenoyl, arachidonoyl, etc. Also useful in place of lecithins are lecithin-based compounds such as lyso-lecithins, in which  $\text{R}^2$  is replaced by hydrogen. Lecithins are described in Kirk-Othmer, Encyclopedia of Chemical Technology, 3rd Ed., Wiley, New York, vol. 14, pp. 250-269 (1981), which is incorporated herein by reference.

In this embodiment, the lecithin functions as both the transfer and the active agent. The Examples given below in which lecithin is used alone, in conjunction with waxy materials, demonstrate a physical protective barrier which apparently does not kill bacteria but discourages its adsorption onto the protective barrier-coating. Lecithin does not kill the bacteria as evidenced by the fact that it can be added to a bacteria-rich broth without inhibiting their growth and vigor, but when lecithin is present on the surface - when it is compounded in a protective physical barrier - the *Strep. mutans* is dissuaded or prevented from adsorbing onto the protected surface.

#### THE BARRIER FUNCTION

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Now having a mechanism for adhering a protective, hydrophobic material to the hydrophilic dental substrate, any of several barrier materials may be selected to perform this function. A microcrystalline wax, for example, is a component in a barrier composition which provides an adherent, conformal, hydrophobic, continuous, inert, colorless or near-colorless barrier which, on application and with subsequent smearing or disturbance, is forced into pits, fissures, cracks and other irregularities of tooth surfaces, thus blocking those sites most vulnerable to occupation by undesirable bacteria and other debris. This waxy barrier appears to endure in place and function indefinitely or until it is mechanically removed. Thus, with the transfer and barrier functions performed, extended protection is provided against deleterious activities since the treated dental surfaces are entirely sealed against bacteria, acids, staining materials, loss of dental fluorine, etc.

In use, the barrier material is brushed or rubbed, on application and thereafter, into pits, cracks, concavities and other depressions. Importantly, barrier materials are amorphous materials which shear or cleave easily so that materials which may adhere to the surface of the barrier may be removed easily by the application of moderate shear forces such as are applied by the action of the tongue against dental surfaces, toothbrushing, dental flossing, forced water cleaning or vigorous mouth rinsing. This same

low-shear characteristic moves the barrier materials about, exposing any active agent substances blended into the barrier materials.

### Hydrophobic Barrier Materials

It has been found that various hydrophobic compounds of high molecular weight, solid at body temperature and generally similar to fats and oils are useful as barrier forming materials. Typically they are long chain hydrocarbons, especially normal paraffins having a chain length of 16 carbons or greater, paraffins with several loci of branching and unsaturation, where the extent of such branching and unsaturation does not create unacceptable toxicity nor lower the solidification point below body temperature, and show essentially no solubility in water or saliva. The major types of these wax-like materials belong to two basic categories:

I. Natural waxes of animal, vegetable or mineral origin such as beeswax, lanolin, spermaceti, carnauba wax,, petroleum waxes including paraffin waxes, microcrystalline petrolatum and microcrystalline wax; and

II. Synthetic materials including ethylenic polymers such as "Carbowax", polymethylene wax ("Paraflint") and various hydrocarbon types as obtained via Fisher-Tropsch synthesis.

Other suitable materials include silicone-based polymers such as polymethylalkylsiloxane, polydimethylsiloxane, poly(perfluoroalkylmethyl siloxane), poly(methyl-3,3,3-trifluoropropyl siloxane) and various aromatic (phenyl containing) siloxanes as sold by Petrarch, which is now United Chemical.

Also useful are various fluoropolymers where some or all of the hydrogen is replaced by fluorine, including, among others: polytetrafluoroethylene (PTFE); fluorinated polyethylene-propylene (FEP); polyvinylidene fluoride (PVDF); and polyvinylfluoride (PVF).

These polymers can be applied to a dental appliance as aqueous or non-aqueous dispersions.

In another embodiment, the present composition contains:

- (a') 0.25 to 25 wt.%, preferably 1 to 5 wt.%, based on the total weight of (a'), (b'), and (c'), of a transfer agent;
- (b') 50 to 99.5 wt.%, preferably 85 to 98 wt.%, based on the total weight of (a'), (b'), and (c'), of a barrier material; and
- (c') 0.25 to 25 wt.%, preferably 1 to 10 wt.%, based on the total weight of (a'), (b'), and (c'), of an active agent.

THE ACTIVE-AGENT (A-A) FUNCTION

Experimentation with the technology of the present invention demonstrates that some types of materials inhibit or defeat the attachment and/or propagation, growth or colonization of bacteria on dental surfaces. The bacteria with which the experiments were performed, *Streptococcus mutans*, and *Streptococcus sobrinus*, are shown to be major sources of bacterial plaque colonies and their sequelae.

Among the materials which demonstrably perform the A-A function are various cetyl amines, nitroparaffin derivatives, duomeens, ethoxylated duomeens, and other quaternary ammonium compounds. Especially useful is 5-Amino-1,3-bis (2-ethylhexyl)-5-methylhexahydropyrimidine, such as is obtainable from Angus Chemical Co. by the tradename hexetidine. Also useful are lecithins which perform important A-A functions.

In addition, the innovative materials whose novel benefits and compositions are described and claimed for the first time in this disclosure/application are useful as Active Agents. These include polyethyleneimines to which fatty acids such as oleic acid, etc. have been added.

Some of the A-A materials tested and described in the Examples below migrated out or diffused away from the areas on which a Protective Coating was applied so that, to some extent, the A-A function extended to areas not reached by the PC itself.

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These A-A materials may be blended into the barrier material so that, as the barrier material is sheared, cleaved, disturbed, eroded, abraded, etc., fresh A-A material is exposed and freed to function.

#### Active Agent Materials

Various compounds which possess antibacterial activity (i.e. are germicides) and some compounds which are not germicides can be used in compositions of the present invention to counter bacterial attachment, development of caries, and plaque information. Examples of applicable antimicrobial agents belong to the following types.

##### a) Amine-free compounds

halogenated salicylanilides, as described in U.S. Patent No. 5,344,641, including:

4',5-dibromosalicylanilide  
3,4',5-trichlorosalicylanilide  
3,4',5-tribromosalicylanilide  
2,3,3',5-tetrachlorosalicylanilide  
3,3,3',5-tetrachlorosalicylanilide  
3,5-dibromo-3'-trifluoromethyl salicylanilide  
5-n-octanoyl-3'-trifluoromethyl salicylanilide  
3,5-dibromo-4'-trifluoromethyl salicylanilide  
3,5-dibromo-3'-trifluoromethyl salicylanilide (fluorophene)

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Benzoic Esters

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Methyl	p-Hydroxybenzoic Ester
Ethyl	p-Hydroxybenzoic Ester
Propyl	p-Hydroxybenzoic Ester
Butyl	p-Hydroxybenzoic Ester

halogenated diphenyl ethers, as described in U.S. Patent No. 5,344,641, including:

2',4,4'-trichloro-2-hydroxy-diphenyl ether (Triclosan)  
2,2'-dihydroxy-5,5'-dibromo-diphenyl ether.

halogenated carbanilides, as described in U.S. Patent No. 5,344,641, including:

3,4,4'-trichlorocarbanilide  
3-trifluoromethyl-4,4'-dichlorocarbanilide  
3,3,4'-trichlorocarbanilide

Also included are phenolic compounds, representative examples of which are described in U.S. Patent No. 5,290,541, which includes phenol, its derivatives and bisphenolic compounds. Specifically, they include:

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 Ph nol and its Homologs
 

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Phenol	-Phenol
2 Methyl	-Phenol
3 Methyl	-Phenol
4 Methyl	-Phenol
4 Ethyl	-Phenol
2,4-Dimethyl	-Phenol
2,5-Dimethyl	-Phenol
3,4-Dimethyl	-Phenol
2,6-Dimethyl	-Phenol
4-n-Propyl	-Phenol
4-n-Butyl	-Phenol
4-n-Amyl	-Phenol
4-tert-Amyl	-Phenol
4-n-Hexyl	-Phenol
4-n-Heptyl	-Phenol

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2-Methoxy-4-(2-Propenyl)-Phenol (Eugenol)  
 2-Isopropyl-5-Methyl-Phenol (Thymol)

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 Mono- and Poly-Alkyl and Aralkyl Halophenols
 

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Methyl	-p-Chlorophenol
Ethyl	-p-Chlorophenol
n-Propyl	-p-Chlorophenol
n-Butyl	-p-Chlorophenol
n-Amyl	-p-Chlorophenol
sec-Amyl	-p-Chlorophenol
n-Hexyl	-p-Chlorophenol
Cyclohexyl	-p-Chlorophenol
n-Heptyl	-p-Chlorophenol
n-Octyl	-p-Chlorophenol

O-Chlorophenol

Methyl	-o-Chlorophenol
Ethyl	-o-Chlorophenol
n-Propyl	-o-Chlorophenol
n-Butyl	-o-Chlorophenol
n-Amyl	-o-Chlorophenol
tert-Amyl	-o-Chlorophenol
n-Hexyl	-o-Chlorophenol
n-Heptyl	-o-Chlorophenol



p-Chlorophenol

o-Benzyl  
o-Benzyl-m-methyl  
o-Benzyl-m,m-dimethyl  
o-Phenylethyl  
o-Phenylethyl-m-methyl  
3-Methyl  
3,5-Dimethyl  
6-Ethyl-3-methyl  
6-n-Propyl-3-methyl  
6-iso-Propyl-3-methyl  
2-Ethyl-3,5-dimethyl  
6-sec-Butyl-3-methyl  
2-iso-Propyl-3,5-dimethyl  
6-Diethylmethyl-3-methyl  
6-iso-Propyl-2-ethyl-3-methyl  
2-sec-Amyl-3,5-dimethyl  
2-Diethylmethyl-3,5-dimethyl  
6-sec-Octyl-3-methyl

-p-Chlorophenol  
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-p-Chlorophenol  
-p-Chlorophenol

p-Bromophenol

Methyl  
Ethyl  
n-Propyl  
n-Butyl  
n-Amyl  
sec-Amyl  
n-Hexyl  
cyclohexyl

-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol  
-p-Bromophenol

o-Bromophenol

tert-Amyl  
n-Hexyl  
n-Propyl-m,m-dimethyl

o-Bromophenol  
o-Bromophenol  
o-Bromophenol

2-Phenyl phenol  
4-Chloro-2-methyl phenol  
4-Chloro-3-methyl phenol  
4-Chloro-3,5-dimethyl phenol  
2,4-Dichloro-3,5-dimethyl phenol  
3,4,5,6-Tetrabromo-2-methylphenol  
5-Methyl-2-pentylphenol  
4-Isopropyl-3-methylphenol  
5-Chloro-2-hydroxydiphenyl methane

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**Resorcinol and its Derivatives**


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Resorcinol	-Resorcinol
Methyl	-Resorcinol
Ethyl	-Resorcinol
n-Propyl	-Resorcinol
n-Butyl	-Resorcinol
n-Amyl	-Resorcinol
n-Hexyl	-Resorcinol
n-Heptyl	-Resorcinol
n-Octyl	-Resorcinol
n-Nonyl	-Resorcinol
Phenyl	-Resorcinol
Benzyl	-Resorcinol
Phenylethyl	-Resorcinol
Phenylpropyl	-Resorcinol
p-Chlorobenzyl	-Resorcinol
5-Chloro	-2,4-Dihydroxydiphenyl Methane
4'-Chloro	-2,4-Dihydroxydiphenyl Methane
5-Bromo	-2,4-Dihydroxydiphenyl Methane
4'-Bromo	-2,4-Dihydroxydiphenyl Methane

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**Bisphenol A**

2,2'-methylene bis(4-chlorophenol)  
 2,2'-methylene bis(3,4,6-trichlorophenol) (hexachlorophene)  
 2,2'-methylene bis(4-chloro-6-bromophenol)  
 bis(2-hydroxy-3,5-dichlorophenyl) sulfide  
 bis(2-hydroxy-5-chlorobenzyl) sulfide

**b) Amine-containing compounds (mostly quaternary amines)**

Among the most common of these antibacterial  
 quaternary ammonium compounds are:

alkyl dimethylbenzylammonium chloride  
 benzethonium chloride (Hyamine 1622),  
 diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium  
 chloride, and cetyl pyridinium halides (chloride, bromide,  
 iodide, and fluoride).

Other materials of this nature are also mentioned in:

U.S. Patent Nos. 2,984,639, 3,325,402, 3,431,208, and  
 3,703,583, and British Pat. No. 1,319,396.

Further analogous compounds include those in which one or two of the substituents on the quaternary nitrogen has a carbon chain length (typically alkyl group) of some 8 to 20, typically 10 to 18, carbon atoms while the remaining substituents have a lower number of carbon atoms (typically alkyl or benzyl group), such as 1 to 7 carbon atoms, typically methyl or ethyl groups. Typical examples are: dodecyl trimethyl ammonium bromide, and benzyl dimethyl stearyl ammonium chloride.

Preferred antimicrobial materials useful in the present invention belong to the nitroparaffin-derived heterocyclic class of compounds. Examples of such compounds may be classified into the following types:

- monocyclic oxazolidines,
- bicyclic oxalidines,
- polymeric bicyclic oxalidines,
- 1,3-dioxanes, oxazolines,
- oxazolidinones, and
- hexahydropyrimidines [5-amino-1,3-bis(2-ethylhexyl)-5-methyl hexahydropyrimidine which is sold under the trade name "hexetidine" by Angus Chemical Co.].

Other guanine-based antimicrobial substances are:

- 1,6-bis-(p-chlorophenyldiguanidine)hexane, also known by the trade name "chlorhexidine",
- 1,6-di-(2-ethylhexyldiguanidine)hexane known as "alexidine", and
- 1,1'-hexamethylene-bis-{5-(4-fluorophenyl)-diguanidine} also known as "fluorhexidine",

In a preferred embodiment of this invention, a non-aqueous dispersion containing micro-crystalline wax, paraffin oil and hexetidine was prepared. The resulting mixture was applied to a polyamide dental tape by drawing the tape through the dispersion. After drying, the tape was drawn over extracted human teeth and glass rods. Testing and observation evidenced that a substantial, smooth and continuous coating of a waxy barrier film had been applied both to the surfaces of the teeth and the glass rods.

The film was also transferred when the dental and glass surfaces were wetted with water immediately prior to the treatment. The hydrophobic films of applied material were not removed by brushing them with ten strokes of a toothbrush while submerged in water.

In another preferred embodiment the present composition comprises:

(a") 0.25 to 25 wt.%, preferably 2 to 5 wt.%, based on the total weight of (a"), (b"), and (c"), of lecithin;

(b") 50 to 99.50 wt.%, preferably 85 to 97.5 wt.%, based on the total weight of (a"), (b"), and (c"), of a barrier material; and

(c") 0.25 to 25 wt.%, preferably 0.5 to 10 wt.%, based on the total weight of (a"), (b"), and (c"), of an active agent.

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In this embodiment, the active agent is preferably selected from the group consisting of hex tidine and chlorhexidines.

When one of the germicidal materials is used together with the lecithin, the bacteria are inhibited (or possibly actually killed at higher concentrations) in a small area surrounding the transferred film. That is, there is some migration or extension of the inhibiting effect. This extended effect is not observed when lecithin is used without an anti-bacterial ingredient.

As alluded to above, the present compositions may further comprise a source of fluoride, such as sodium fluoride, potassium fluoride, tin fluoride, zinc fluoride, organic fluorides such as long-chained aminofluorides, for example oleylamino fluoride, cetyl aminofluoride or ethanolaminohydrofluoride, fluorosilicates, for example, potassium hexafluorosilicate or sodium hexafluorosilicate, fluorophosphates such as ammonium, sodium, potassium, magnesium or calcium fluorophosphate and/or fluoro zirconates, for example sodium, potassium or tin fluoro zirconate. The present compositions may also further comprise one or more antibiotics, such as penicillin, polymyxin B, vancomycin, kanamycin, erythromycin, niddamycin, metronidazole, spiramycin and tetracycline.

The present composition may also include a flavoring ingredient to mask any odor or taste of the other ingredients. Examples of such flavorings include oils

and/or aromatic/flavorant materials such as cinnamon, lemon, lime, orange, spearmint, peppermint, clove, almond etc. The flavorant may be present in an amount conventionally used for imparting the desired flavor, typically 0.01 to 5 wt.%, preferably 0.05 to 2 wt.%, based on the total weight of the composition.

The present compositions may be prepared by a method in which the barrier material is first suspended or dissolved in an appropriate solvent (e.g. xylene, toluene, petroleum ether, methanol, ethanol, methyl ethyl ketone, or where, for example, aqueous dispersions of fluorocarbons are selected as barrier materials, water). The transfer agent and, optionally, active agent(s) are then added and the solvent removed by, e.g., evaporation.

The present dental delivery systems may be prepared by coating a suitable substrate (dental floss, toothbrush, toothpick, etc.) with the present composition. This may conveniently be carried out by dipping the substrate in the suspension or solution containing the barrier material, transfer agent, and optionally, active agent referred to above in connection with the preparation of the present compositions, and then drying the substrate to remove the solvent, leaving a coating of the present composition on the substrate. Alternatively, the dry composition prepared above may be redissolved or resuspended, and the substrate dipped in the thus-formed solution or suspension, followed by solvent removal.

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Most conveniently, the present compositions may be used and applied in the same manner as a conventional toothpaste and squeezed from a tube onto a toothbrush or other appliance; or the compositions may be packaged in a box or other container from which the composition may be applied to a toothbrush by the brush being passed over and into the composition. Should modification of the viscosity of the present compositions be desirable, an appropriate diluent may be included in the composition. Suitable diluents include one or more of the following oils which are listed with the temperatures (°C) at which they become solids: cottonseed oil (+12 to -13); corn oil (-10 to -20); cod liver oil (-3); olive oil (+2 to -6); beech nut oil (-17); peanut oil (3); poppyseed oil (-16); rape seed oil (also called Canola oil) (-10); safflower oil (-1); sesame oil (-10); soya (-10); sunflower (-17); walnut (-27); white mustard seed oil (-10); whale oil; polyethylene glycols and silicone oils of appropriate molecular weight; and some other such may also be useful. These oils may be added in an amount of up to 50 wt.% or even more, preferably 10 to 50 wt.%, based on the total weight of the composition to achieve the desired characteristics.

Additionally and importantly, compositions of the present invention may be compounded as oil-in-water micro-emulsions or colloidal dispersions, which may be suitably prepared by methods well known to those experienced in the field.

The present method of protecting the teeth may be carried out by contacting the present dental delivery system with the teeth to effect transfer of the composition from the dental delivery system to the surface of the teeth. The exact means of contacting will depend of course on the nature of the dental delivery system. Thus, in the case of toothpaste, brushing will suffice to apply the compositions while masticables will be applied as the act of chewing applies and compresses the compositions onto and into the surfaces of the teeth, while dental floss requires flossing and toothpicks, swabs and other appliances will require rubbing or smearing actions for applications.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

#### EXAMPLES

In the following examples, and throughout this specification, all parts and percentages are by weight, and all temperatures are in degrees Celsius, unless expressly stated to be otherwise. Where the solids content of a dispersion or solution is reported, it expresses the weight of solids based on the total weight of the dispersion or solution, respectively. Where a molecular weight is specified, it is the molecular weight range ascribed to the product by the commercial supplier, which is identified.



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Generally this is believed to be weight average molecular weight.

In all of the following examples in which teeth are mentioned, the teeth are extracted human teeth which were professionally cleaned with abrasives, sterilized by multiple autoclaving and, prior to use in the following examples, hydrated in distilled water for at least one hour. Immediately prior to use the teeth were immersed in and withdrawn from a mixture of distilled water and fresh human saliva (at approximately 1:1 by volume), so that the treated surfaces were wet at the time of application of materials.

Example I:

43 Grams of xylene solvent sold by EM Science, 5 grams of microcrystalline wax sold by Calwax under the trade designation Victory White and 2 grams of paraffin oil, Saybolt viscosity 340-355, sold by EM Science, were heated to approx. 50°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature and 0.125 grams of N-tallow-1,3-propanediamine sold by Akzo under the trade designation Duomeen TDO (as transfer agent) were admixed by stirring. The result was a mixture in which the microcrystalline wax appeared to be uniformly dispersed but not dissolved in the solvent. A cotton tipped applicator was dipped into this mixture and the solvent was allowed to evaporate at an elevated

temperature of about 50°C. The coated applicator was then rubbed against a tooth surface until a smooth and water-repelling film was obtained, the tooth surface having been wetted with a 1:1 by volume mixture of distilled water and fresh human saliva immediately prior to the application of the coated applicator (see Figure 3).

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water.

#### *In vitro* Demonstration of Efficacy

The bacteria adsorption-inhibiting ability of each formulation thus obtained was evaluated as follows: A pure culture of bacteria obtained from American Type Culture Collection (ATCC), (designated ATCC # 27607, and identified as *Streptococcus sobrinus*, the same organisms having also and previously been designated and identified as *Streptococcus mutans*), was maintained by subculturing onto fresh brain-heart-infusion agar plates and incubating in a CO<sub>2</sub> incubator at 37°C. To prepare a testing medium, a small quantity of bacteria was transferred into 4 ml of brain-heart infusion (BHI) liquid medium (obtained from Curtin Matheson) and incubated for 24 hours at 37°C. After the incubation period, the concentration of the bacteria in the inoculum was adjusted, with sterilized BHI medium, to about

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$2 \times 10^7$  cells/ml ( $OD_{560} = 0.02$ ). The contact bacteria solution (0.3 ml) of the above was added to 30 ml of BHI medium containing 4% sucrose and shaken at 120 strokes/minute for 3 minutes. The tested samples of untreated teeth and teeth coated with the transfer film were then placed into the inoculated medium and incubated under anaerobic conditions at 37°C for 48 hours. After removal from the medium, the teeth were rinsed in water and stained with Crystal Violet stain. Examination by microscopy revealed significant inhibition of bacterial adherence in the areas covered by the transferred films as compared with the untreated control surfaces which were covered by heavy deposits of adherent bacteria.

Example II:

A mixture was prepared as described in Example I. A polyamide dental floss, as manufactured for Johnson & Johnson, Inc., was drawn through and vertically out of the mixture at a rate of about 3 mm per second, the thickness of the coating being controlled by the rate at which the floss was drawn through the mixture. Following air drying at an elevated temperature, a short strand of the floss, approx. 2 feet in length, was drawn back and forth across the tooth surfaces (extracted human central incisors), imitating a normal flossing procedure, until a uniform and tenaciously adhering film was produced (see Figure 7). The film exhibited a high degree of hydrophobicity as attested

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by measurements of contact angles in excess of 90°. Adherence of bacteria to the tooth surfaces was evaluated according to the procedure outlined in Example I. A significant inhibition of bacterial adherence to the transferred film was observed.

#### Example III:

A mixture was prepared as described in Example I. Wooden toothpicks were immersed in the mixture and slowly withdrawn. After drying at room temperature, toothpicks were rubbed over wetted extracted tooth surfaces until a smooth and continuous film was formed. Further, in order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on a film surface. Repeated measurements of the contact angles showed values in excess of 90° indicating a high degree of hydrophobicity of the interface. Exposure of the treated teeth to the bacteria media for 48 hours or more demonstrated a significant reduction in bacteria adsorption, comparable to the reduction observed in Examples I and II.

#### Example IV:

A mixture was prepared as described in Example I. Ordinary toothbrushes, some of the bristles of which were "natural" fibers, and some nylon, were immersed in the mixture and withdrawn at a rate of about 3 mm/sec. After drying at an elevated temperature, the toothbrushes were

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drawn back and forth several times over the tooth surfaces, simulating the action and movement of toothbrushing (see Figure 5).

Treated surfaces of the teeth were then observed by microscope. Substantial, smooth and continuous layers of the deposited waxy material appeared on the tooth surfaces. Further, in order to determine the degree of hydrophobicity imparted by the waxy films, drops of water were deposited on the transferred films and the contact angles measured. Repeated measurements showed values in excess of  $90^\circ$  indicating the high degree of hydrophobicity of the surfaces. A significant inhibition of bacterial adherence to the transferred film was observed.

Example V:

43 Grams of xylene solvent sold by EM Science, 5 grams of microcrystalline wax sold by Calwax under the trade designation Victory White and 2 grams of paraffin oil, Saybolt viscosity 340-355, sold by EM Science, were heated to approx.  $50^\circ\text{C}$  and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.2 grams of cetyl amine sold by Aldrich (as transfer agent) were admixed by stirring. The result was a mixture in which the microcrystalline wax appeared to be uniformly dispersed but not completely dissolved in the solvent. A cotton tipped applicator was dipped into this mixture and withdrawn, and the solvent was

allowed to evaporate at an elevated temperature. The coated applicator was then rubbed against the wetted glass slide until a smooth and water-repelling film was obtained.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film and the contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water.

Adherence of bacteria to the tooth surfaces was evaluated according to the procedure outlined in Example I. A significant inhibition of bacterial adherence to the barrier film was observed.

#### Example VI:

A mixture was prepared as described in Example V. A polyamide dental floss, as manufactured for Johnson & Johnson, Inc., was drawn through and vertically out of the mixture at a rate of about 3 mm per second, the thickness of the coating being controlled by the rate at which the floss was drawn through the mixture. Following air drying at an elevated temperature, a short strand of the floss, approx. 2 feet in length, was drawn back and forth across the tooth surfaces, imitating a normal flossing procedure, until a uniform and tenaciously adhering film was produced. The film exhibited a high degree of hydrophobicity as attested by measurements of contact angles in excess of

90°. Adherence of bacteria to the tooth surfaces was evaluated according to the procedure outlined in Example I. A significant inhibition of bacterial adherence to the barrier film was observed.

Example VII:

A mixture was prepared as described in Example V. Wooden toothpicks were immersed in the mixture and slowly withdrawn. After drying at room temperature, the toothpicks were rubbed repeatedly over wetted tooth surfaces until a smooth and continuous film was formed. Further, in order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the film surface and the contact angles were measured. Repeated measurements showed values in excess of 90° indicating a high degree of hydrophobicity of the interface. Exposure of the treated teeth to bacterial media resulted in a significant reduction in bacteria adsorption comparable to the reduction observed in Examples V and VI.

Example VIII:

A mixture was prepared as described in Example V. Ordinary toothbrushes, some of the bristles of which "natural" fibers, and some nylon, were immersed in the mixture and slowly withdrawn. After drying at an elevated temperature, the toothbrushes were drawn back and forth

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several times over wetted tooth surfaces, simulating the action and movement of toothbrushing. The treated surfaces of the teeth were then observed by microscope. Substantial, smooth and continuous layers of the deposited waxy material appeared on the tooth surfaces. Further, in order to determine the degree of hydrophobicity imparted by the waxy films, drops of water were deposited on the transferred films and the contact angles measured. Repeated measurements showed values in excess of  $90^\circ$  indicating the high degree of hydrophobicity of the surfaces. Incubation for 48 hours in bacterial media showed a significant inhibition of bacterial adherence. Further, it was noted that subsequent brushing, while both the tooth and toothbrush were immersed in water, resulted in complete removal of bacteria from the waxy film while the surrounding untreated areas remained covered by bacterial colonies.

Enhancement of the Inhibition of Bacterial Attachment and/or Propagation, Growth and Colonization:

A significant enhancement in efficacy of the barrier film to inhibit adherence of bacterial colonies was realized when various antibacterial agents such as hexetidine, for example, were incorporated into the formulation. Examples IX through XII demonstrate the effectiveness of this approach.



Example IX:

43 Grams of xylene solvent sold by EM Science, 5 grams of microcrystalline wax sold by Calwax under the trade designation Victory White and 2 grams of paraffin oil, Saybolt viscosity 340-355, sold by EM Science, were heated to approx. 50°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.3 grams of Duomeen TDO (AKZO Chemical Co.) (as transfer agent) were admixed by stirring. To this mixture, 1.25 grams of 5-Amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine sold by Angus Chemical Co., under the trade designation of hexetidine (as active agent) was added with vigorous mixing. The result was a mixture in which the microcrystalline wax appeared to be uniformly dispersed but not dissolved. A cotton tipped applicator was dipped into this mixture, and the solvent was allowed to evaporate from it at an elevated temperature. The coated applicator was then rubbed against a glass slide until a smooth and water-repelling film was obtained, the slide having been wetted with distilled water immediately prior to the application of the applicator.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film, and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water. The ability of the barrier film to inhibit

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adsorption of bacteria was evaluated as described in Example I. A negligible number of bacterial colonies, as compared with the untreated control areas adjacent to the film were observed even after 4 days exposure to the bacteria bearing media.

Example X:

A mixture was prepared as described in Example IX. A polyamide dental floss, as manufactured for Johnson & Johnson, Inc., was drawn through and vertically out of the mixture at a rate of about 3 mm per second, the thickness of the coating being controlled by the rate at which the floss was drawn through the mixture. Following air drying at an elevated temperature, a short strand of the floss, approx. 2 feet in length, was drawn back and forth across tooth surfaces (human central incisors), imitating a normal flossing procedure, until a uniform and tenaciously adhering film was produced. The film exhibited a high degree of hydrophobicity as attested by measurements of contact angles in excess of 90°. Adherence of bacteria to the treated tooth surfaces was evaluated according to the procedure outlined in Example I. Examination by microscopy (Figures 8a and 8b) revealed that the area covered by the transferred film was essentially free of bacterial colonies while the surrounding non-treated control areas were covered by heavy deposits of adsorbed bacteria.

Example XI:

A mixture was prepared as described in Example IX. Wooden toothpicks were immersed in the mixture and withdrawn. After drying at room temperature, toothpicks were rubbed repeatedly over wetted tooth surfaces until a smooth and continuous film was formed. Further, in order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the film surface, and the contact angles measured. Repeated measurements showed values in excess of  $90^\circ$  indicating a high degree of hydrophobicity of the interface. Exposure of the treated teeth to bacterial media resulted in a negligible amount of isolated bacterial colonies adhering to the film surface.

Example XII:

A mixture was prepared as described in Example IX. Ordinary toothbrushes, some of the bristles of which were "natural" fibers, and some nylon, were immersed in the mixture and slowly withdrawn. After drying at an elevated temperature, the toothbrushes were drawn back and forth several times over wetted tooth surfaces, simulating the action and movement of toothbrushing. The treated surfaces of the teeth were then observed by microscope. Substantial, smooth and continuous layers of the deposited waxy material appeared on the tooth surfaces. Further, in order to determine the degree of hydrophobicity imparted by

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the waxy films, drops of water were deposited on the transferred films, and the contact angles were measured. Repeated measurements showed values in excess of  $90^\circ$  indicating the high degree of hydrophobicity of the surfaces. Incubation for 48 hours in bacterial media showed a high resistance of the film to react with any components of the media including bacteria (Figures 6a and 6b). Microscopic observations failed to detect any residual bacteria or bacterial colonies after the treated tooth surfaces were gently brushed with a toothbrush under running tap water.

Example XIII:

83.5 Grams of xylene solvent sold by EM Science, 10 grams of microcrystalline wax sold by Calwax under the trade designation Victory White and 4 grams of paraffin oil, Saybolt viscosity 340-355, sold by EM Science, were heated to approximately  $50^\circ\text{C}$  and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. To this mixture, 2.5 grams of 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine sold by Angus Chemical Co., under the trade designation of hexetidine (as transfer agent and active agent) was added with vigorous mixing. The result was a mixture in which the microcrystalline wax appeared to be uniformly dispersed but not completely dissolved. A cotton tipped applicator was dipped into this mixture, and the solvent was allowed

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to evaporate at an elevated temperature (40-50°C). The cotton applicator was then rubbed against tooth surfaces until a smooth and water-repelling film was obtained.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film and contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water.

Adherence of bacteria to the treated surfaces was evaluated according to the procedure outlined in Example I. Examination by microscopy showed that treated surface areas of teeth were essentially free of adsorbed bacteria while untreated control surfaces were laden with heavy deposits of adhered bacterial colonies (Figures 4a and 4b).

Example XIV:

84.75 Grams of xylene solvent sold by EM Science, 10 grams of microcrystalline wax sold by Calwax under the trade designation Victory White and 4 grams of paraffin oil, Saybolt viscosity 340-355, sold by EM Science, were heated to approximately 50°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. To this mixture, 1.25 grams of N-tallow-1,3-propanediamine dioleate sold by Akzo Nobel Chemicals Inc., under the trade designation of Duomeen TDO (as transfer agent and active agent) was added with vigorous mixing. The result was a mixture in which the

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microcrystalline wax appeared to be uniformly dispersed but not completely dissolved. A cotton tipped applicator was dipped into this mixture and the solvent was allowed to evaporate at an elevated temperature (40-50°C). The cotton applicator was then rubbed against a glass slide until a smooth and water-repelling film was obtained.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film and contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water.

Adherence of bacteria to the barrier film was evaluated according to the procedure outlined in Example I. A significant inhibition of bacterial adherence to the barrier film was observed.

Example XV:

4.3 Grams of polyethyleneimine (1/10 segmental molecular weight) and 15.2 grams of stearyl chloride (1/20 mol) are dissolved in 25 ml of ethanol and refluxed gently for 30 minutes. After cooling to room temperature, 25 ml of 25% aqueous solution of silver fluoride is added and the mixture is stirred for 10 minutes. The precipitated silver chloride is filtered off, and the crude derivative is purified by crystallization. The crystalline derivative is transferred to a plastic beaker and dissolved in 25 ml of ethanol. 3.0 Grams of 40% hydrofluoric acid (1/20 mol +

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20%) are added to the solution and the whole is then evaporated on a water bath until its consistency is paste-like. The remaining solvent is driven out in vacuo at about 50°C. The compound remains as a colorless slightly brownish paste. It is soluble in alcohols and hydrocarbon-based solvents.

Example XVI:

2 Grams of micro-crystalline wax (sold by Calwax under the trade designation, "Victory White") and 0.5 g of paraffin oil, Saybolt viscosity 340-355, sold by E. M. Science, were heated to approximately 80°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.5 g of 25% lecithin extract (Type XV-E from fresh frozen egg yolk, Sigma Chem Co.) in MEK and 0.01 g of cinnamon oil were added. The mixture was warmed to 80°C and mixed until a clear solution was obtained and then allowed to cool to room temperature. The result was a mixture in which lecithin appeared to be uniformly dispersed but not dissolved. The MEK solvent was removed by heating the mixture to 50°C for several hours.

A cotton swab applicator (Q-tip-like) was wiped across the now semi-solid, waxy mixture, coating the swab. The swab was then rubbed against a wet-with-water slide until a patent, water-repelling, film was observed to be transferred to the glass slide.

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In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film, and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water. The ability of the barrier film to inhibit adsorption of bacteria was evaluated as described in Example I. In this case, no bacterial colonies, as compared with the untreated control areas adjacent to the film, were observed even after 4 days exposure to the bacteria-bearing media.

Example XVII:

2 Grams of micro-crystalline wax (sold by Calwax under the trade designation, "Victory White") and 0.5 g of paraffin oil, Saybolt viscosity 340-355, sold by E. M. Science, were heated to approximately 80°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.5 g of 25% lecithin extract (Type XV-E from fresh frozen egg yolk, Sigma Chem Co.) in MEK, together with 0.05 g of hexetidine (Angus Chemical Co.) and 0.01 g of cinnamon oil were added. The mixture was warmed to 80°C and mixed until a clear solution was obtained and then allowed to cool to room temperature. The MEK solvent was removed by heating the mixture to 50°C for several hours.



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A cotton swab applicator (Q-tip-like) was wiped across the now-solid mixture and subsequently rubbed against a slide, wetted with water, until a patent, water-repelling, film was observed to be transferred to the glass slide.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film, and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water. The ability of the barrier film to inhibit adsorption of bacteria was evaluated as described in Example I. In this case, no bacterial colonies, as compared with the untreated control areas adjacent to the film, were observed even after 4 days exposure to the bacteria-bearing media.

Example XVIII:

22.5 Grams of MEK solvent sold by E.M. Science, 2.0 g of micro-crystalline wax (sold by Calwax under the trade designation, "Victory White"), and 0.5 g of paraffin oil, Saybolt viscosity 340-355, sold by E.M. Science, were heated to approximately 50°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.5 g of 25% lecithin extract (Type XV-E from fresh frozen egg yolk, Sigma Chemical Co.) in MEK, and 0.01 g of cinnamon oil were added.

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A polyamide dental floss, as manufactured for Johnson & Johnson, Inc. was drawn through the mixture at a rate of about 3 mm per second, the thickness of the coating being controlled by the rate at which the floss was drawn through the mixture. Following air drying at an elevated temperature, a strand of the floss, approximately 2 feet in length, was wadded up and the wad then rubbed across a wet glass microscope slide until an adherent film was observed to be transferred. The film exhibited a high degree of hydrophobicity as attested to by the measurement of contact angles in excess of 90°. Adherence of bacteria to the treated slides was evaluated according to the procedure outlined in Example I. Examination by microscopy revealed that the area covered by the transferred film was essentially free of bacterial colonies while the surrounding non-treated control areas were covered by heavy deposits of adsorbed bacteria.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film, and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water. The ability of the barrier film to inhibit adsorption of bacteria was evaluated as described in Example I. In this case, no bacterial colonies, as compared with the untreated control areas adjacent to the

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film, were observed even after 4 days exposure to the bacteria-bearing media.

Example XIX:

A mixture was prepared as described in Example XVI. Ordinary toothbrushes, some of the bristles of which were "natural" fibers, and some of which were nylon, were brushed across the semi-solid mixture. The coated toothbrushes were then brushed across a wet microscope slide, simulating the action and movement of toothbrushing. Substantial and continuous layers of the waxy mixture material were transferred to the wet microscope slide. Further, in order to determine the degree of hydrophobicity imparted by the waxy films, drops of water were deposited on the transferred films, and the contact angles were measured. Repeated measurements showed values in excess of 90° indicating the high degree of hydrophobicity of the surfaces. Incubation for 48 hours in bacterial media showed a high resistance of the film to react with any components of the media including bacteria. Microscopic observations failed to detect any residual bacteria or bacterial colonies after the treated slides were gently brushed with a toothbrush under running tap water.

Example XX:

2 Grams of micro-crystalline wax (sold by Calwax under the trade designation, "Victory White") and 0.5 g of

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paraffin oil, Saybolt viscosity 340-355, sold by E. M. Science, were heated to approx 80°C and vigorously mixed until a clear solution was produced. The mixture was allowed to cool to room temperature. Then, 0.5 g of 25% lecithin extract (Type IV-S from soybean, Sigma Chem Co.) in MEK and 0.01 g of cinnamon oil were added. The mixture was warmed to 80°C and mixed until a clear solution was obtained and then allowed to cool to room temperature. The MEK solvent was removed by heating the mixture to 50°C for several hours.

A cotton swab applicator (Q-tip-like) was wiped across the now semi-solid, waxy mixture, coating the swab. The swab was then rubbed against a wet-with-water slide until a patent, water-repelling, film was observed to be transferred to the glass slide.

In order to determine the degree of hydrophobicity imparted by the waxy film, drops of water were deposited on the surface of the film, and their contact angles were measured. Repeated measurements showed values in excess of 90° indicating a strong tendency of the surface to repel water. The ability of the barrier film to inhibit adsorption of bacteria was evaluated as described in Example I. In this case, no bacterial colonies, as compared with the untreated control areas adjacent to the film, were observed even after 4 days exposure to the bacteria-bearing media.

Example XXI

Two grams of paraffin oil (Seybolt), 1.8 grams of hexetidine (Angus Chemical Co.), and 0.4 grams of chlorhexidine powder 99% (Aldrich Chemical Co. catalog #34,803-1), were vigorously mixed until a good dispersion was produced. Then 2 grams of chewing gum base ('Dreyco', L.A. Dreyfus Corp., P.O. Box 500 South Plainfield, NJ), 6 grams of microcrystalline wax (Victory White, Calwax, Azusa, CA) were heated until melted at -85°C, and to that mixture the first mixture was added and mixed until a homogenous mixture was obtained.

Adherence of bacteria to the tooth surfaces was evaluated according to the procedure outlined in Example I. A highly significant inhibition of bacterial adherence to the barrier film was observed.

To determine the efficacy of the composition in inhibiting the development of caries when applied in vivo to teeth, a rat caries trial was conducted.

The goal of the trial was to test whether once-daily, 5 day/week brief applications of one of the compositions of the present invention to the teeth of rats will result in reduction of plaque bacterial numbers, *S. mutans* numbers, and dental caries in *S. mutans*-colonized Specific Pathogen Free Osborne-Mendel rats eating a high sucrose diet known to foster plaque formation and dental caries. Twenty animals were used as controls and twenty as experimentals over the 43 day trial period. The results of the trial

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indicate that the present composition potently reduces recoveries of oral flora, more potently reduces recoveries of *S. mutans*, and is potently anticariogenic. Of course, experimental animals eat many times daily and retain food in the fissures of their teeth. Indeed, one must expect the cariogenic challenge to be severe in these locations, and it is noteworthy that compositions of the present invention had so much effectiveness there, albeit less so than on smooth surfaces of teeth which mechanically retain little food. For total (i.e. smooth surface + sulcal) enamel lesions, scores were reduced by 55% for hemimandibular and 40% for maxillary teeth respectively; for total dentinal lesions, scores were reduced by 60% for hemimandibular and 54% for maxillary teeth, respectively, where caries were scored by the method of Keyes (1958), as modified by Larson (1981). These differences are highly statistically significant.

It should be noted that the occlusal surfaces of the rats teeth were constantly filled and impacted with hair, food and other debris and that no attempt was made to remove any of it at any time during the trial. It is expected that even more dramatically beneficial results will be obtained in human trials in which at least gross debris, food particles, etc. are removed on a regular basis so that the composition of the present invention can be applied into the occlusal pits and fissures.

Example XXII

Three grams of microcrystalline wax (Victory White, Calwax Corp., Azusa, CA), 2 grams of gum base (Dreyco, from L.A. Dreyfus Co., P.O. Box 500. South Plainfield, NJ), and 2 grams of paraffin oil were heated and mixed until a homogenous mixture was obtained. To this mixture was added 0.07 grams of hexetidine and 0.1 grams of peppermint oil and stirred until homogenous. The composition was applied to extracted teeth with a cotton swab and the procedure described above was followed.

Adherence of bacteria to the tooth surfaces was evaluated according to the procedure outlines in Example I. A highly significant inhibition of bacterial adherence to the barrier film was observed.

Hexetidine and the issue of its solubility in the oral cavity in compositions of the present invention.

An important issue is the quantity of hexetidine, used in Examples XXI and XXII as both transfer and active agent, which is soluble in saliva and available to the tissues of the oral cavity and digestive tract is swallowed. A comparison with other products containing hexetidine is useful. Mouthrinses or mouthwashes containing 0.12% by wt. of hexetidine in a soluble form have been sold for many years in many countries including the United States, Canada, most of western Europe, and several Asian countries. The dosage or quantity of mouthrinse typically

used in such calculations is 20 ml per application, with two applications per day being a standard recommendation. At 0.12% concentration, 24 mg of soluble hexetidine per application is available to interact with tissues of the oral cavity and digestive tract of the consumer.

By comparison, the composition of the present invention used in Example XXI, delivers 7.5 mg of insoluble hexetidine per 50 mg dose, delivered by brush to typical human consumers. Only a minute fraction of the hexetidine can enter the saliva since the material is essentially insoluble. In addition, the great majority of the hexetidine is immobilized and encapsulated in the waxy matrix.

In the composition of the present invention used in Example XXII, 0.5 mg of hexetidine is contained in the typical 50 mg dose used in toothbrushing, most of which is captured in the waxy matrix and what little may be available at the surface of the composition is essentially insoluble and therefore unavailable to the saliva or tissues of the oral cavity.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.



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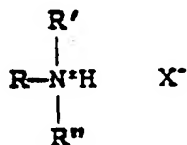
All patents and other references mentioned above are incorporated in full herein by this reference, the same as if set forth at length.

## CLAIMS:

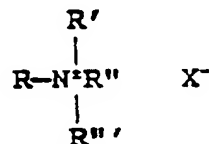
1. A composition, comprising:
  - (a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of transfer agent; and
  - (b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material.
2. The composition of Claim 1, comprising 3 to 5 wt.%, based on the total weight of (a) and (b), of said transfer agent and 95 to 97 wt.%, based on the total weight of (a) and (b), of said barrier material.
3. The composition of Claim 1, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



-- (III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics;

polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_4O]_X H_2(+)$  A(-), where A(-) is chloride or fluoride, X is a number from 1 to 20, and R is a  $C_{8-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

4. The composition of Claim 1, wherein said barrier material is a microcrystalline wax.

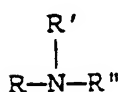
5. The composition of Claim 1, which is a toothpaste or chewing gum.

6. A composition comprising:

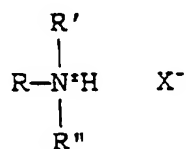
- (a") 0.25 to 25 wt.%, based on the total weight of (a"), (b"), and (c"), of a transfer agent;
- (b") 50 to 99.50 wt.%, based on the total weight of (a"), (b"), and (c"), of a barrier material; and
- (c") 0.25 to 25 wt.%, based on the total weight of (a"), (b"), and (c"), of an active agent.

7. The composition of Claim 6, comprising 1 to 5 wt.%, based on the total weight of (a"), (b"), and (c"), of said transfer agent, 85 to 98 wt.%, based on the total weight of (a"), (b"), and (c"), of said barrier material, and 1 to 10 wt.%, based on the total weight of (a"), (b"), and (c"), of said active agent.

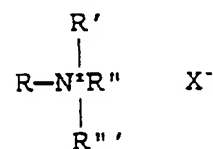
8. The composition of Claim 6, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy

groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_4O]_xH_2(+) A(-)$ , where A(-) is chloride or fluoride, X is a number from 1 to 20, and R is a C<sub>8-22</sub> alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a C<sub>8-20</sub> fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a C<sub>8-20</sub> fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

9. The composition of Claim 6. wherein said barrier material is a microcrystalline wax.

10. The composition of Claim 6, wherein said active agent is selected from the group consisting of hexetidine and chlorhexidine.

11. The composition of Claim 6, which is a toothpaste or chewing gum.

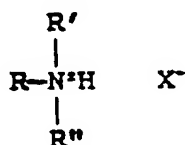
12. A method of protecting teeth, comprising treating teeth with a composition comprising:

- (a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of transfer agent; and
- (b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material.

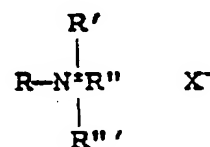
13. A method of Claim 12, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide;

cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_5O]_xH_2(+) A(-)$ , where  $A(-)$  is chloride or fluoride,  $x$  is a number from 1 to 20, and  $R$  is a  $C_{8-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

14. The method of Claim 12, wherein said barrier material is a microcrystalline wax.

15. The method of Claim 12, wherein said composition is a toothpaste or a chewing gum.

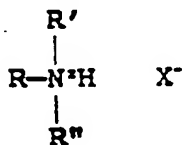
16. A method of protecting teeth, comprising treating teeth with a composition comprising:

- (a'') 0.25 to 25 wt.%, based on the total weight of (a''), (b''), and (c''), of a transfer agent;
- (b'') 50 to 99.5 wt.%, based on the total weight of (a''), (b''), and (c''), of a barrier material; and
- (c'') 0.25 to 25 wt.%, based on the total weight of (a''), (b''), and (c''), of an active agent.

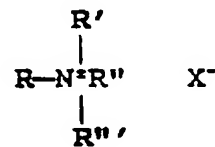
17. The method of Claim 16, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>3-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>1-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics;



polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_4O]_xH_2(+) A(-)$ , where  $A(-)$  is chloride or fluoride,  $x$  is a number from 1 to 20, and  $R$  is a  $C_{8-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

18. The method of Claim 16, wherein said barrier material is a microcrystalline wax.

19. The method of Claim 16, wherein said active agent is selected from the group consisting of hexetidine and chlorhexidine.

20. The method of Claim 16, wherein said composition is a toothpaste or a chewing gum.

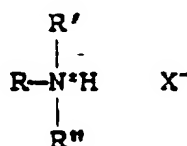
21. A dental delivery system, comprising a substrate coated with a composition comprising:

- (a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of a transfer agent; and
- (b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material.

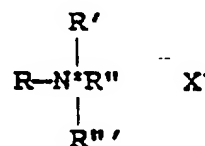
22. The dental delivery system of Claim 21, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene

biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyl-laurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_4O]_xH_2(+) A(-)$ , where  $A(-)$  is chloride or fluoride.  $x$  is a number from 1 to 20, and  $R$  is a  $C_{8-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

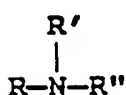
23. The dental delivery system of Claim 21, wherein said barrier material is a microcrystalline wax.

24. A dental delivery system, comprising a substrate coated with a composition comprising:

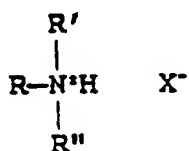
(a") 0.25 to 25 wt.%, based on the total weight of (a"), (b"), and (c"), transfer agent;

- (b') 50 to 99.5 wt.%, based on the total weight of (a''), (b''), and (c''), of a barrier material; and
- (c'') 0.25 to 25 wt.%, based on the total weight of (a''), (b''), and (c''), of an active agent.

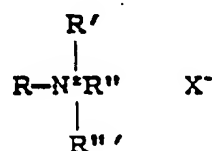
25. The dental delivery system of Claim 24, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines;

polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_5O]_XH_2(+) A(-)$ , where  $A(-)$  is chloride or fluoride,  $X$  is a number from 1 to 20, and  $R$  is a  $C_{8-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{8-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

26. The dental delivery system of Claim 24, wherein said barrier material is a microcrystalline wax.

27. The dental delivery system of Claim 24, wherein said active agent is selected from the group consisting of hexetidine and chlorhexidine.

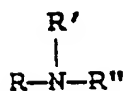
28. A method for alleviating the sensitivity of teeth, comprising treating sensitive teeth with a composition comprising:

- (a) 0.25 to 25 wt.%, based on the total weight of (a) and (b), of transfer agent; and

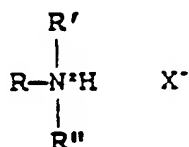
- (b) 75 to 99.75 wt.%, based on the total weight of (a) and (b), of a barrier material.

29. The method of Claim 28, comprising 3 to 5 wt.%, based on the total weight of (a) and (b), of said transfer agent and 95 to 97 wt.%, based on the total weight of (a) and (b), of said barrier material.

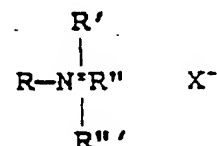
30. The method of Claim 28, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide; cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorides, polyhexamethylene biguanides; 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides,

poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_2H_4O]_xH_2(+) A(-)$ , where  $A(-)$  is chloride or fluoride,  $x$  is a number from 1 to 20, and  $R$  is a  $C_{1-22}$  alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{1-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a  $C_{1-20}$  fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

31. The method of Claim 28, wherein said barrier material is a microcrystalline wax.

32. The method of Claim 28; which is a toothpaste or chewing gum.

33. A method for alleviating the sensitivity of teeth comprising treating sensitive teeth with a composition comprising:

(a") 0.25 to 25 wt.%, based on the total weight of (a"), (b"), and (c"), of a transfer agent;

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(b") 50 to 99.50 wt.%, based on the total weight of (a"), (b"), and (c"), of a barrier material; and

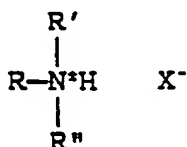
(c") 0.25 to 25 wt.%, based on the total weight of (a"), (b"), and (c"), of an active agent.

34. The method of Claim 33, comprising 1 to 5 wt.%, based on the total weight of (a"), (b"), and (c"), of said transfer agent, 85 to 98 wt.%, based on the total weight of (a"), (b"), and (c"), of said barrier material, and 1 to 10 wt.%, based on the total weight of (a"), (b"), and (c"), of said active agent.

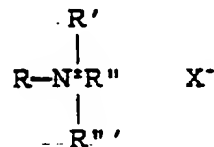
35. The method of Claim 33, wherein said transfer agent is selected from the group consisting of compounds of the formulae (I), (II), and (III):



(I)



(II)



(III)

wherein R is a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, R', R'', and R''' each independently are a C<sub>8-20</sub> alkyl chain which may be substituted with one or more hydroxy groups, a C<sub>1-4</sub> alkyl group which may be substituted with one or more hydroxy groups, a C<sub>6-10</sub> aryl group, or hydrogen, and X is fluoride or chloride; laurylpyridinium chloride; laurylpyridinium bromide; cetylpyridinium chloride; cetylpyridinium bromide;



cetylpyridinium fluoride; petroleum derived cationics; polydimeryl polyamines; polyamides; polyacrylamides; polydiallyl dimethylammonium chlorid s, polyhexamethylene biguanides: 1,5-dimethyl-1,5-diazaundecamethylene polymethobromide; polyvinylpyrrolidones; polypeptides, poly(allylamine)hydrochloride; polyoxyethylenated amines; polyethyleneimines; acylated polyethyleneimines; diethylaminoethyl cellulose; poly(vinyl-benzylstearylbetaine); poly(vinyl-benzylmethyl-laurylammonium chloride); poly(vinyl-benzyllaurylpyridylpyridinium chloride); poly(vinyl-benzylcetylammonylhexyl ether); compounds of the formula  $RN(CH_3)[CC_7H_{13}O]_xH_2(+)$  A(-), where A(-) is chloride or fluoride, X is a number from 1 to 20, and R is a C<sub>8-22</sub> alkyl group; polyacrylamide in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a C<sub>8-20</sub> fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; polyvinylpyridine in which 5 to 95 mole% of the nitrogen atoms have been derivatized by reaction with a C<sub>8-20</sub> fatty acid halide and 5 to 95 mole% of the nitrogen atoms have been quaternized with HF; and 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine.

36. The method of Claim 33, wherein said barrier material is a microcrystalline wax.

37. The method of Claim 33, wherein said active agent is a water-soluble desensitizing agent.

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38. The method of Claim 33, which is a toothpaste or chewing gum.

39. The method of Claim 33, wherein said active agent is contained in a microporous particulate.

40. The composition of Claim 1, which is in the form of a confection.

41. The composition of Claim 6, which is in the form of a confection.

42. A method of treating and/or preventing gingivitis, comprising applying to teeth the composition of Claim 1.

43. A method of treating and/or preventing gingivitis, comprising applying to teeth the composition of Claim 6.

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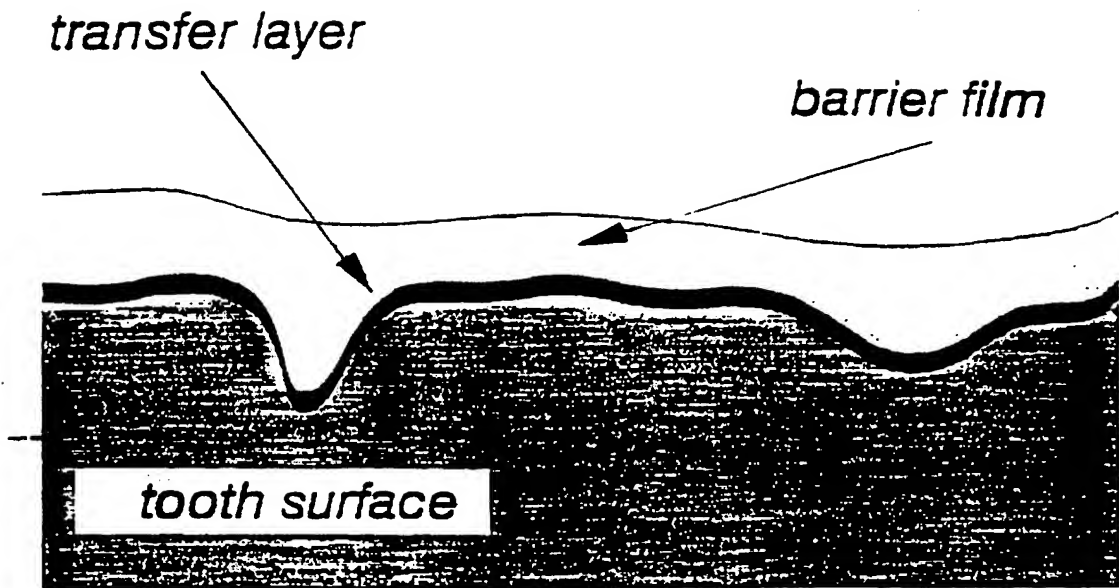
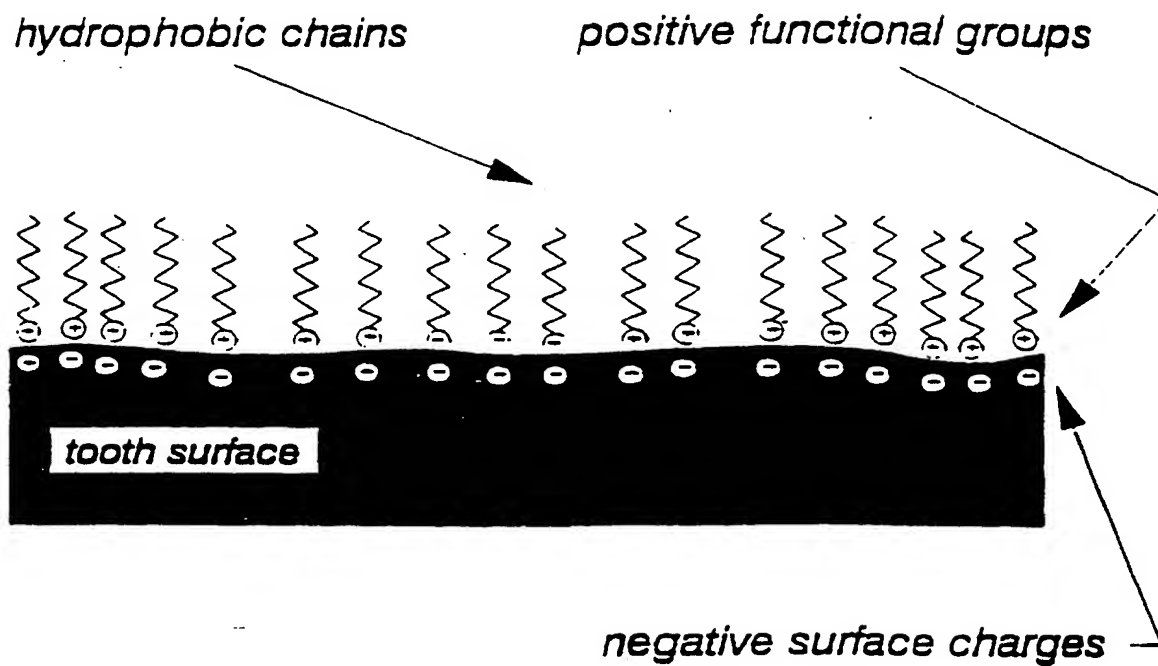


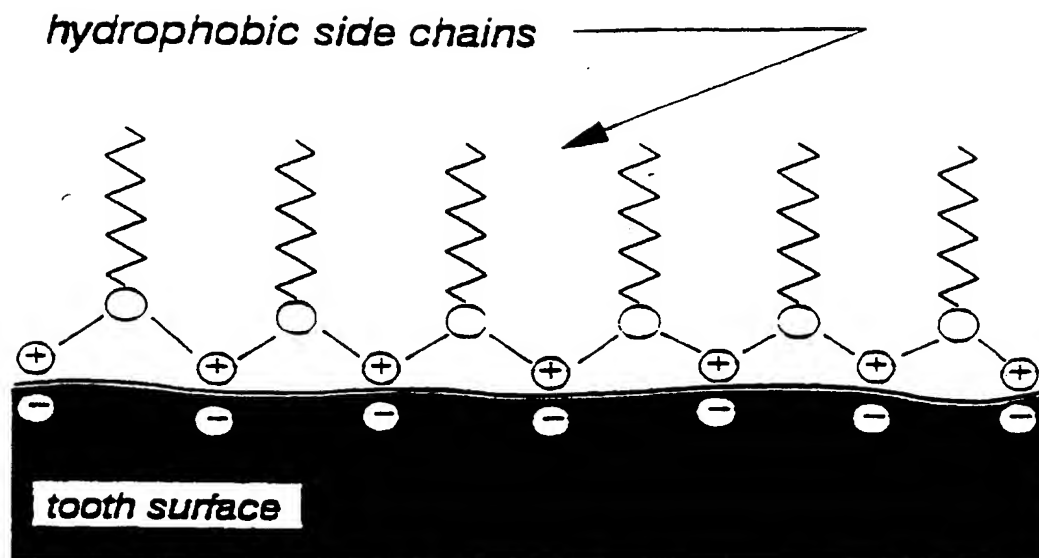
Figure 1

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a



b



Figures 2a and b

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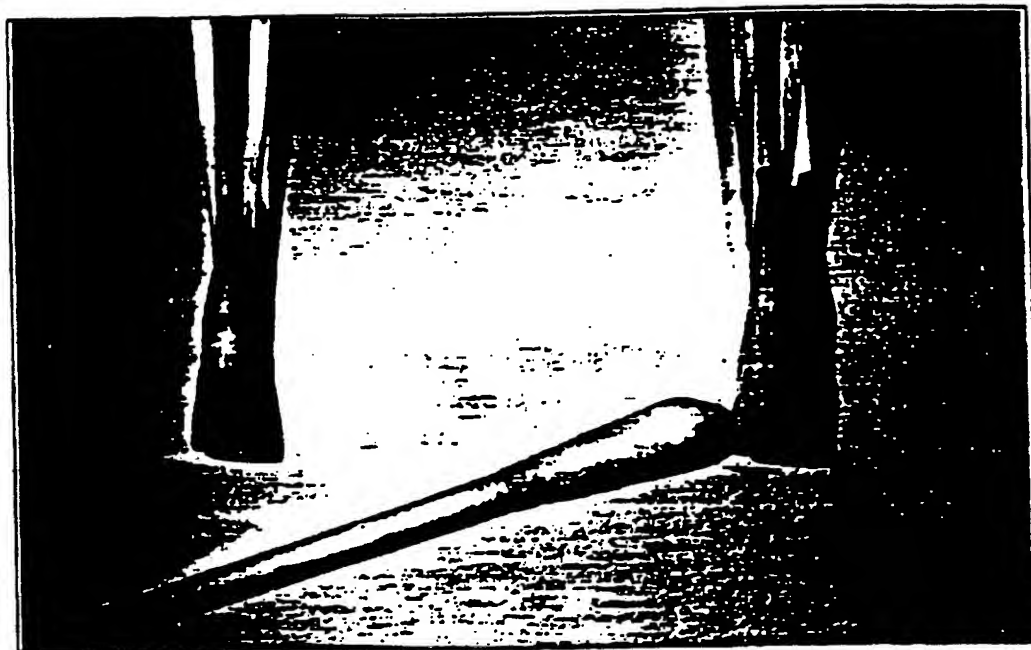
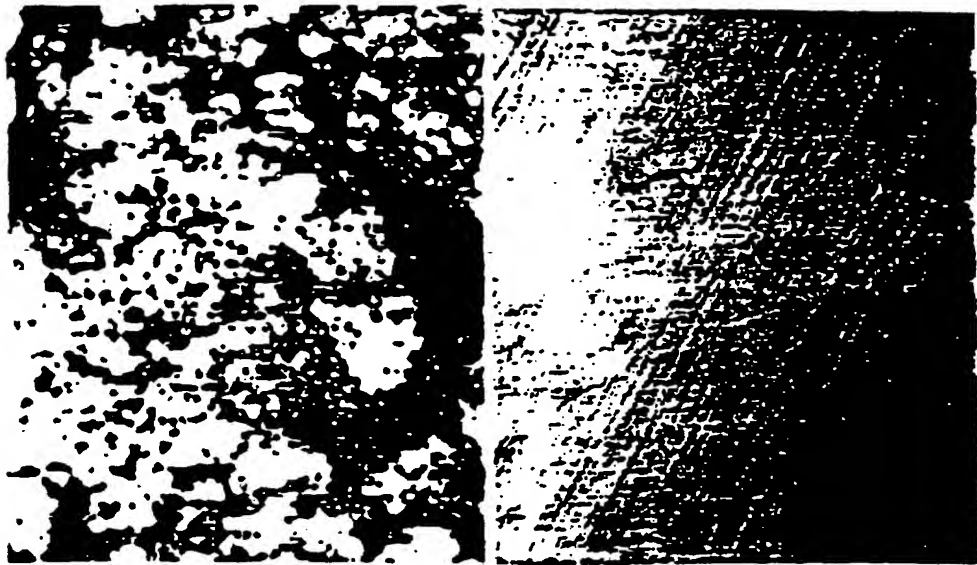


Figure 3

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a

b

Figures 4a and b

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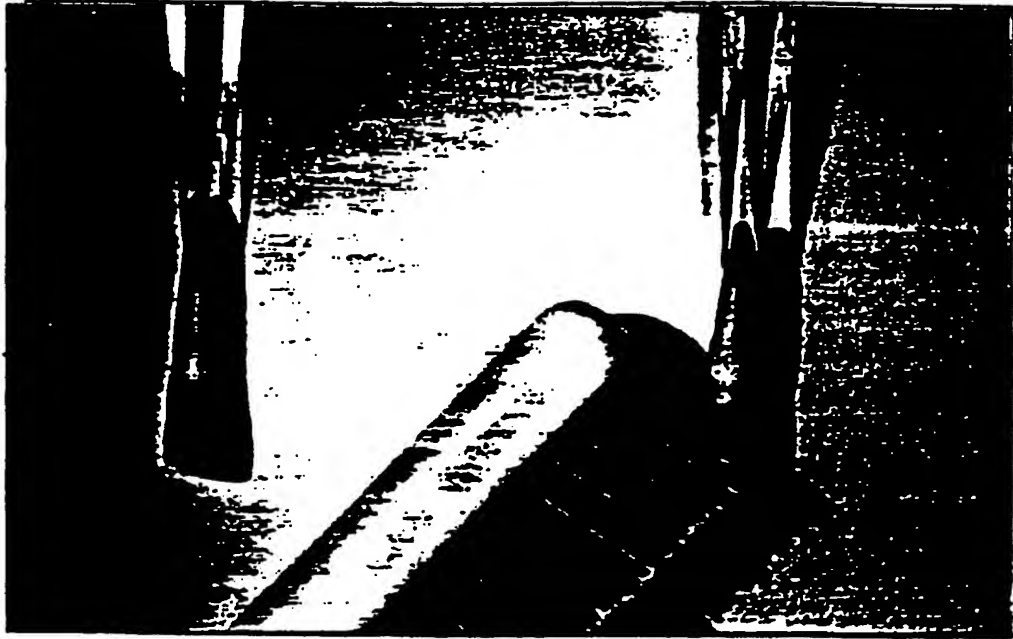
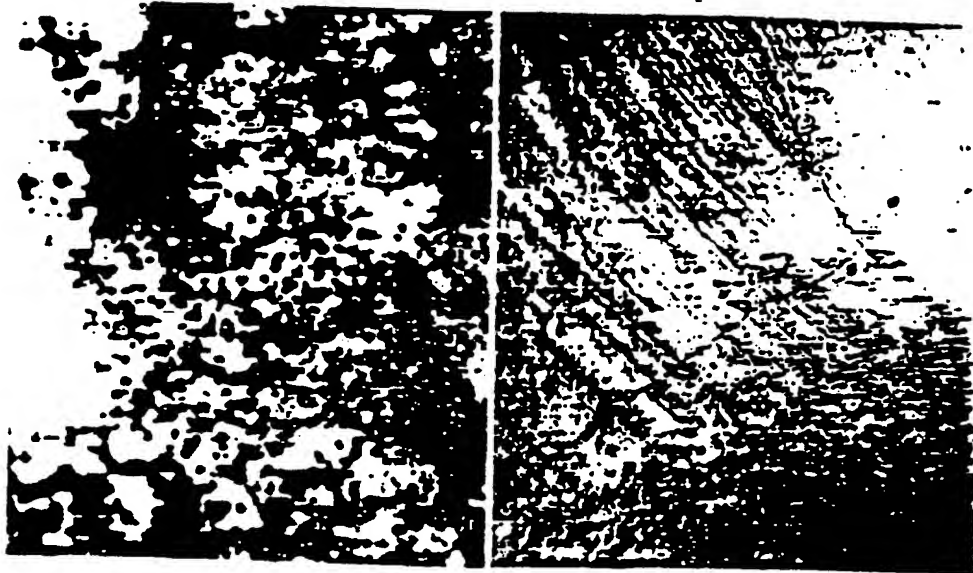


Figure 5

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a

b

Figures 6a and b



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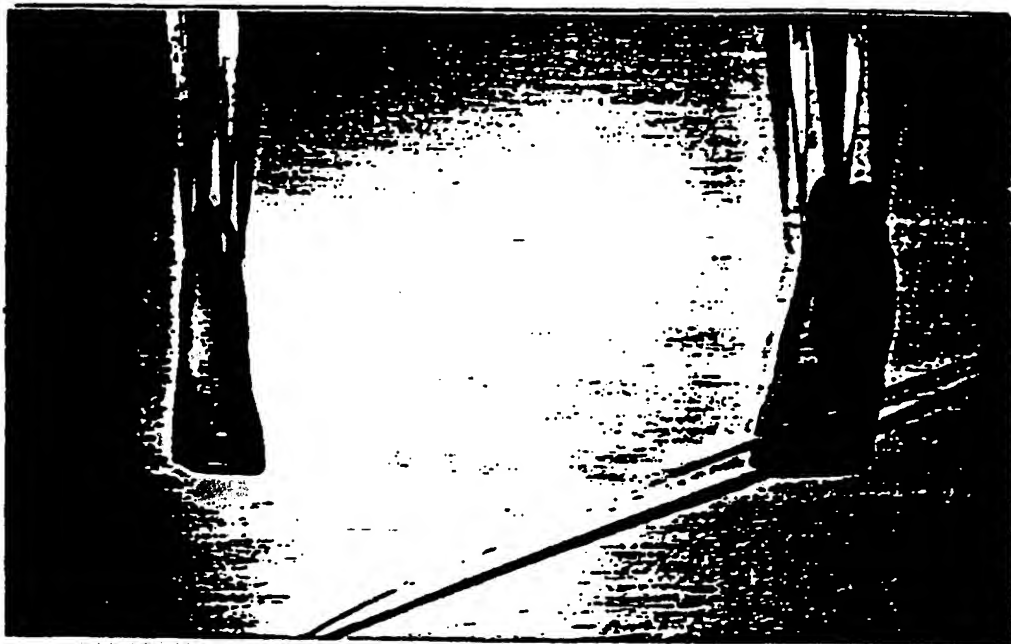
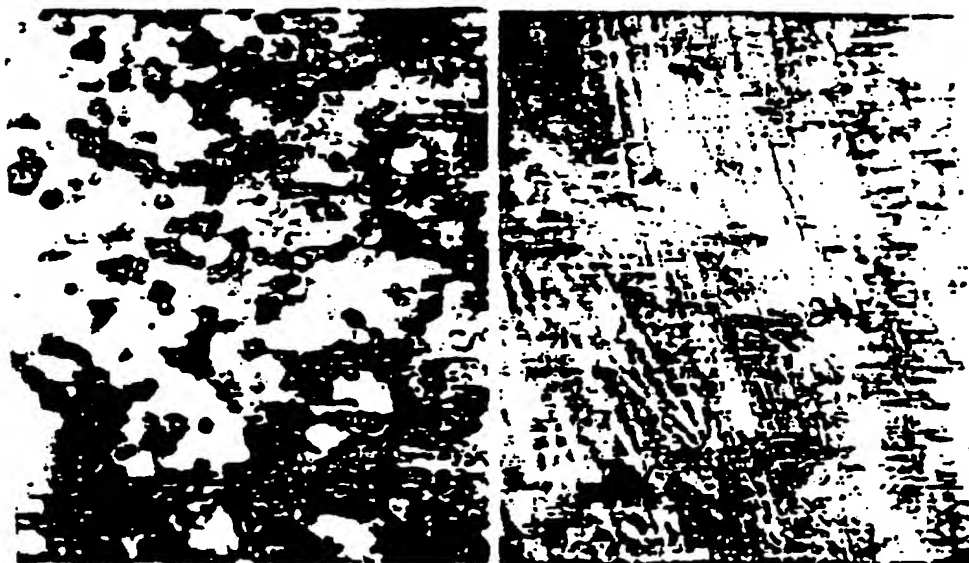


Figure 7

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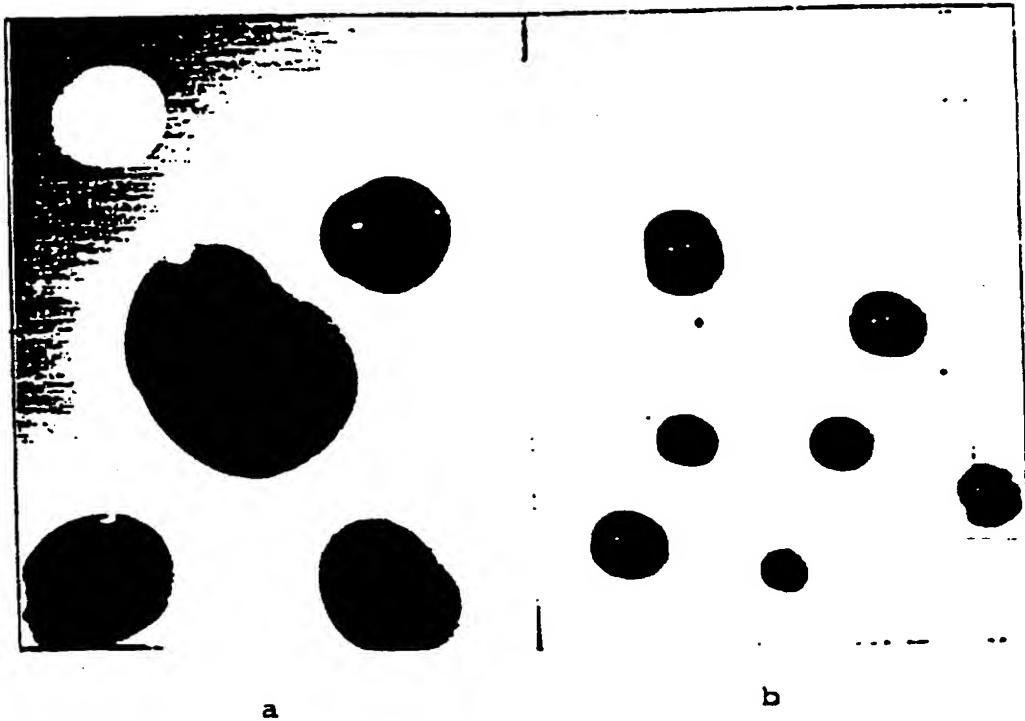


a

b

Figures 8a and b

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Figures 9a and b

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/12496

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 7/40, 6/00, 7/16, 9/68, 47/00

US CL : 424/443, 48, 49, 401; 514/787; 427/2.29, 175; 428/40.1, 343

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/443, 48, 49, 401; 514/787; 427/2.29, 175; 428/40.1, 343

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, REGISTRY, CA, CAPLUS, MEDLINE, EMBASE, WPIDS, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,380,530 A (HILL) 10 January 1995, see the entire document.	1-43
X	US 4,528,182 A (CURTIS et al.) 09 July 1985, see the entire document.	1-43
Y	US 4,911,927 A (HILL et al.) 27 March 1990, see the entire document.	1-43

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

22 AUGUST 1997

Date of mailing of the international search report

28 OCT 1997

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